ENSPRYNG®
satralizumab-mwge
subcutaneous injection 120 mg/mL



WHEN IT COMES TO TREATING AQP4-IgG(+) NMOSD,

DULL MOMENTS AREN'T SUCH A BAD THING.

Life with NMOSD is unpredictable; ENSPRYNG helps by reducing the risk of relapse with an established long-term safety profile.[1-5]

AQP4=aquaporin-4; IgG=immunoglobulin G; NMOSD=neuromyelitis optica spectrum disorder.

Indication and Important Safety Information

Indication

ENSPRYNG is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Contraindications

ENSPRYNG is contraindicated in patients with a known hypersensitivity to satralizumab or any of the inactive ingredients, an active hepatitis B infection, or active or untreated latent tuberculosis.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

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NMOSD is a chronic, debilitating autoimmune disease[6-11]

Approximately **22,000** people in the United States are living with NMOSD[12]

NMOSD is **twice as common** in people with an African or Asian background compared with Caucasians[12,13]

The median age of onset for NMOSD is **32 to 41 years**, but cases are also seen in children and older adults[13]

NMOSD is **9x** more prevalent in females vs males[13]

NMOSD is often associated with pathogenic immunoglobulin G autoantibodies, targeting aquaporin-4 (AQP4-IgG) found in the central nervous system.[11]

- AQP4-IgG antibody production is increased in NMOSD[10]
- **Up to 80%** of patients with NMOSD are AQP4-IgG(+)[11]

Patients with NMOSD are at risk of developing unpredictable, severe relapses that can cause cumulative, irreversible neurologic damage.[2,3]

- **80% to 90%** of patients with NMOSD experience recurring relapses[14]
- Even a single attack is sufficient to cause blindness, paralysis, or death[6,7,9-11,15,16]

Important Safety Information

Warnings and Precautions

Infections

An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG. The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies, and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant, and that occurred more often than in patients receiving placebo, were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%). Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



AQP4-IgG testing is essential when diagnosing NMOSD[17-19]

Approximately 40% of patients with NMOSD are initially misdiagnosed with multiple sclerosis or other diseases, but the presence of the AQP4-IgG antibody serves as a critical distinguishing factor.[19,20]

There are multiple ways to screen for AQP4-IgG in patients with suspected NMOSD[17-19]:

CELL-BASED ASSAY (CBA)

This method uses a substrate and patient sera to detect AQP4 antibodies. **International diagnostic guidelines from 2015 recommend use of CBA whenever possible**, due to the low rate of false positives[19]

M23-ENZYME–LINKED IMMUNOSORBENT ASSAY (ELISA):

This test utilizes the M23 isoform to detect AQP4 antibodies[18]

Early diagnosis through testing is crucial to start treatment and prevent irreversible damage caused by NMOSD relapses[18,19]

Important Safety Information

Warnings and Precautions (cont'd)

Hepatitis B Virus (HBV) Reactivation
Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Alternative diagnoses must be excluded to validate an NMOSD diagnosis[19]

After establishing AQP4 serostatus, 1 core clinical characteristic confirms diagnosis

Core clinical characteristics include[19,21-24]:

- Optic neuritis
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions
- Acute myelitis
- Symptomatic narcolepsy or acute diencephalic clinical syndrome
- Area postrema syndrome
- Acute brainstem syndrome

Important Safety Information

Warnings and Precautions (cont'd)

Tuberculosis

Tuberculosis has occurred in patients treated with other IL-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of signs and symptoms of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Factors to consider when making treatment decisions for your patients with AQP4-IgG(+) NMOSD[25-27]

When selecting an NMOSD treatment, keep these factors in mind alongside patient preference

PATIENT CHARACTERISTICS

- Comorbidities
- Age
- Relapse severity
- Response to prior maintenance therapy
- Concomitant use of ISTs

CLINICAL CHARACTERISTICS

- Mechanism of action
- Efficacy
- Safety
- Treatment guideline recommendations

LOGISTICAL FACTORS

- Route of administration
- Dosing frequency
- Administration time
- Patient proximity to treatment center

FINANCIAL FACTORS

- Insurance coverage
- Cost of treatment
- Patient out-of-pocket cost

Shared decision-making between patients and their healthcare providers can help patients maintain a sense of control and lead to better treatment satisfaction[28]

ISTs=immunosuppressive therapies.

Important Safety Information

Warnings and Precautions (cont'd)

Vaccinations
Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



The treatment landscape for AQP4-IgG(+) NMOSD

Key factors across FDA-approved treatment options to help inform decision-making when choosing a treatment

	ENSPRYNG® (satralizumab-mwge)[1]	SOLIRIS® (eculizumab)[29]	ULTOMIRIS® (ravulizumab-cwvz)[30]	UPLIZNA® (inebilizumab-cdon)[31]
MOA	IL-6 inhibition	C5 inhibition	C5 inhibition	Anti-CD19+ (B-cell depletion)
Administered by	Patient or caregiver*	HCP	HCP	HCP
Administration route	SC injection	IV infusion	IV infusion	IV infusion
Administration time	User-driven	35-minute infusion	~1-hour infusion	90-minute infusion
Starting dose	3 doses over 4 weeks	5 doses over 5 weeks	1 starting dose	2 doses over 2 weeks
Maintenance dose frequency	Q4W	Q2W	Q8W	Q6M

No head-to-head studies have been conducted; therefore, comparisons of safety or effectiveness should not be made. All products are trademarks of their respective owners.

*ENSPRYNG is intended for patient self-administration by SC injection under the guidance of an HCP. After proper training in SC injection technique, a patient or their caregiver may administer ENSPRYNG at home if it is determined to be appropriate.[1,32]

FDA=US Food and Drug Administration; HCP=healthcare provider; IL-6=interleukin-6; IV=intravenous; MOA=mechanism of action; Q2W=every 2 weeks; Q4W=every 4 weeks; Q6M=every 6 months; Q8W=every 8 weeks; SC=subcutaneous.

Important Safety Information

Warnings and Precautions (cont'd)

Elevated Liver Enzymes

Mild and moderate elevations of liver enzymes have been observed in patients treated with ENSPRYNG at a higher incidence than in patients receiving placebo. ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for one year, and thereafter, as clinically indicated.

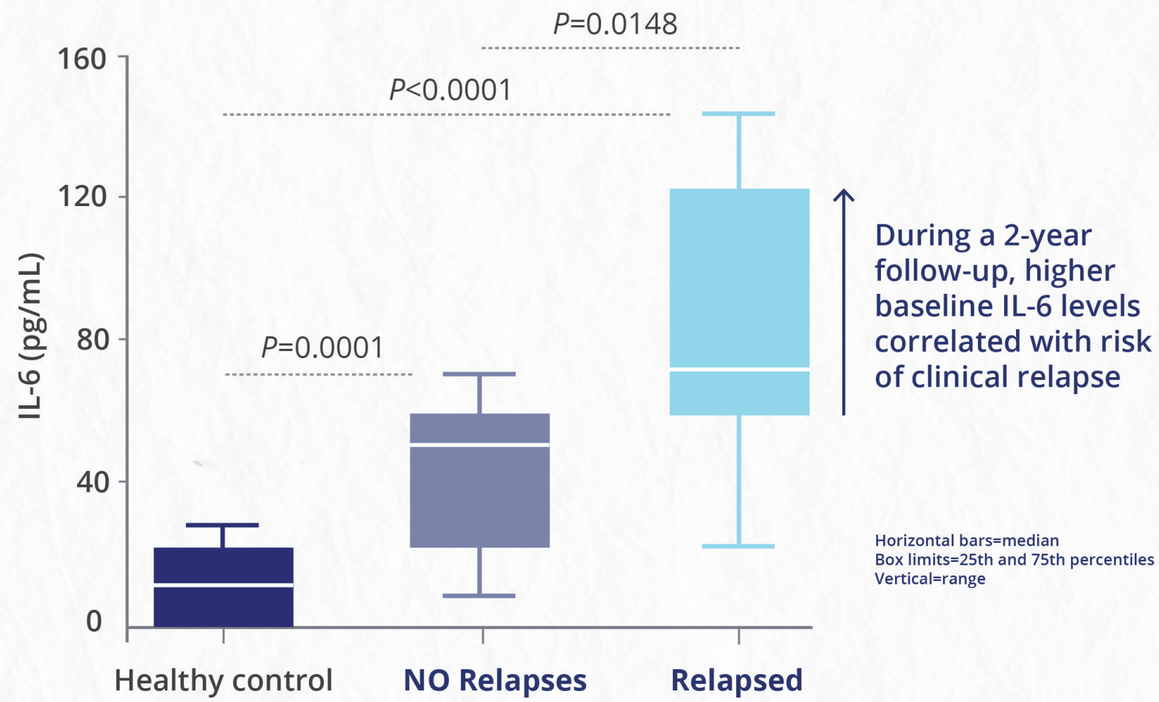
Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Elevated IL-6 levels may be indicative of NMOSD relapse[33]

Due to its role in NMOSD, IL-6 is an important therapeutic target[10,34-36]

Relationship between serum IL-6 levels and NMOSD relapses[33]*



*IL-6 levels were assessed at baseline in patients with neuromyelitis optica (NMO) (n=20) who were in clinical remission and not receiving maintenance treatment. After a 2-year follow-up period, patients were stratified by those without clinical relapse ("NO Relapses"; n=9) and those who had at least 1 relapse ("Relapsed"; n=11). Baseline IL-6 levels were compared between NMO groups and healthy controls (n=20).[33]

IL-6=interleukin-6.

Important Safety Information

Warnings and Precautions (cont'd)

Decreased Neutrophil Counts

Decreases in neutrophil counts were observed in patients treated with ENSPRYNG at a higher incidence than placebo. Neutrophil counts should be monitored 4 to 8 weeks after initiation of therapy, and thereafter at regular clinically determined intervals.

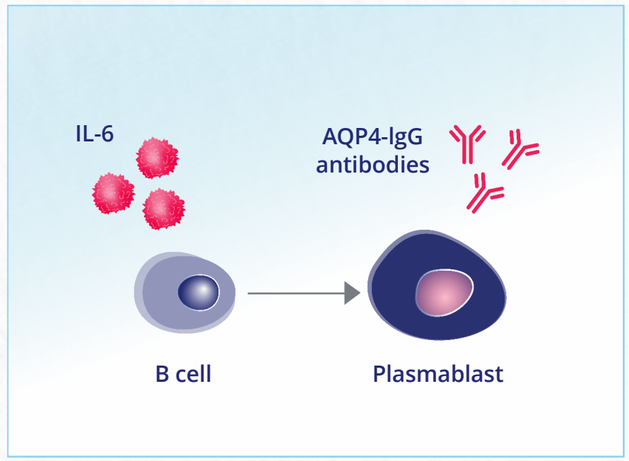
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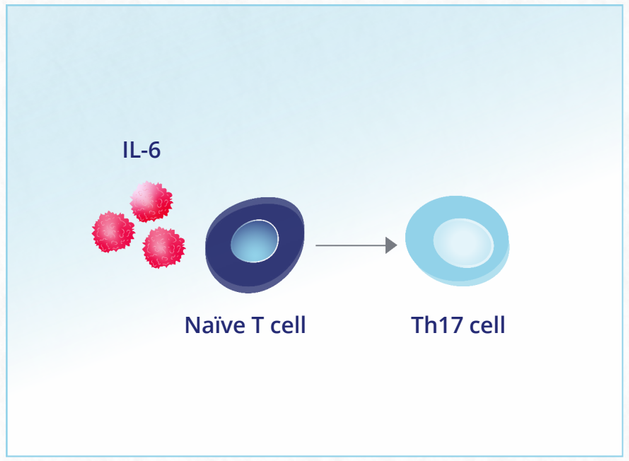


Four functions of IL-6 are implicated in NMOSD progression[10,36]

1 | AQP4-IgG production

IL-6 stimulates the differentiation of B cells to plasmablasts, which secrete AQP4-IgG[10,36]



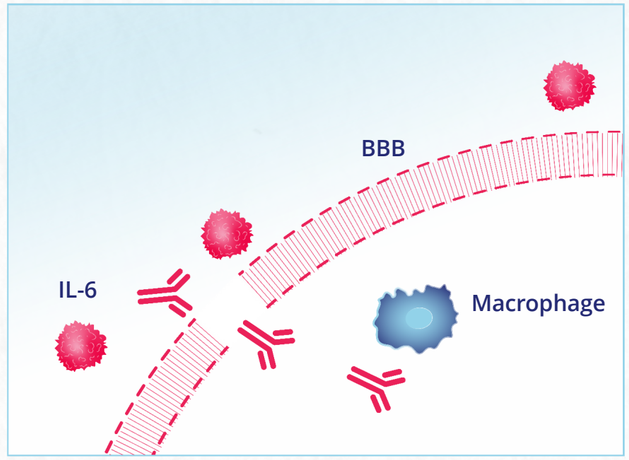


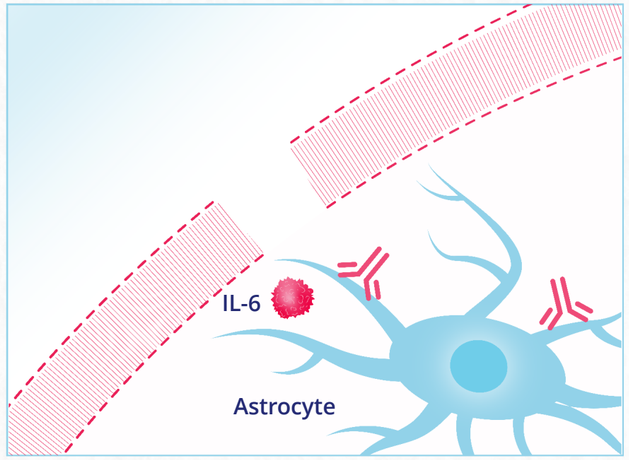
2 | Th17 cell differentiation

IL-6 promotes differentiation into inflammatory Th17 cells, which provide support to AQP4-producing plasmablasts[10,34-36]

3 | BBB permeability

IL-6 increases BBB permeability, allowing penetration of AQP4 antibodies and proinflammatory cells into the central nervous system[10,34-36]





4 | Astrocyte injury and neuronal loss

Once in the brain, AQP4 antibodies bind with AQP4 channels on astrocytes, leading to astrocyte injury via the complement cascade and ultimately leading to demyelination and neuronal loss[10,34-36]

BBB=blood-brain barrier; Th17=T helper 17.

Important Safety Information

Warnings and Precautions (cont'd)

Hypersensitivity Reactions

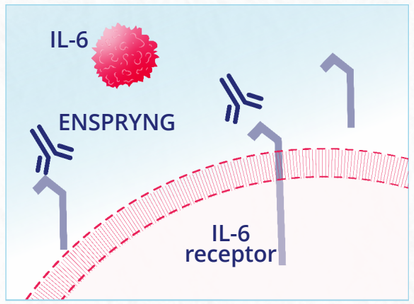
Hypersensitivity reactions, including rash, urticaria, and fatal anaphylaxis, have occurred with other IL-6 receptor antagonists.

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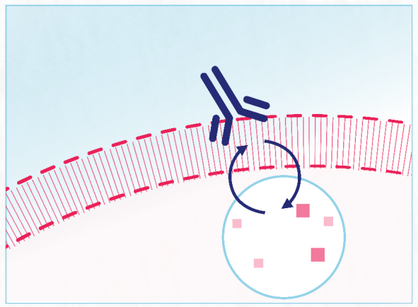
ENSPRYNG modulates the immune response by blocking the IL-6 receptor to treat NMOSD[1,10]

In doing so, ENSPRYNG does not directly affect the innate immune system in the same way that broader ISTs do[1,37-39]



While the precise mechanism by which ENSPRYNG exerts therapeutic effects in NMOSD is unknown, it is presumed to involve inhibition of IL-6-mediated signaling via binding to membrane-bound and soluble IL-6 receptors.[1]

By inhibiting IL-6 signaling, ENSPRYNG is thought to help decrease IL-6-mediated autoimmune T- and B-cell activation and differentiation of B cells into AQP4-IgG-secreting plasmablasts. In turn, this targets inflammation, BBB permeability, and astrocyte injury—all key drivers of NMOSD.[1,10,34-36,40]



ENSPRYNG was designed using **antibody-recycling technology**, which allows it to be recycled back into the bloodstream to bind more antigen, prolonging half-life and enabling sustained suppression of IL-6 signaling.[36]

ISTs=immunosuppressive therapies.

ENSPRYNG is the first and only treatment for AQP4-IgG(+) NMOSD that blocks IL-6 signaling[1,32]

Important Safety Information

Use in Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENSPRYNG during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-277-9338.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

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WHEN IT COMES TO TREATING AQP4-IgG(+) NMOSD,

DULL MOMENTS AREN'T SUCH A BAD THING.

ENSPRYNG is a proven treatment option for NMOSD, as shown through 10+ years of clinical study, including 4+ years of post-approval use[1,41-43]

Important Safety Information

Use in Specific Populations (cont'd)

Pregnancy

Pregnancy Exposure Registry

There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of ENSPRYNG at doses up to 50 mg/kg/week. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



The Neuromyelitis Optica Study Group (NEMOS) 2024 Guidelines recommend ENSPRYNG as a first-line treatment option for NMOSD[25]

Inhibition of IL-6 with ENSPRYNG: over a decade of clinical trial and post-FDA-approval* experience[1,41-43]



Since approval, 5500+ PATIENTS have been treated globally with ENSPRYNG[44]†

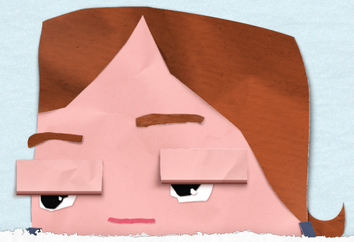
*ENSPRYNG received FDA approval on August 14, 2020.[32]
†Based on individuals with AQP4-IgG(+) NMOSD receiving ENSPRYNG worldwide as of May 2024.[44]
FDA=Food and Drug Administration.

Important Safety Information

Use in Specific Populations (cont'd)

Lactation
No information is available on the presence of ENSPRYNG in human milk, the effects of ENSPRYNG on the breastfed infant, or the effects of ENSPRYNG on milk production. ENSPRYNG was excreted in the milk of lactating monkeys administered ENSPRYNG throughout pregnancy. Human IgG is excreted in human milk and the potential for absorption in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and any potential adverse effects on the breastfed infant from ENSPRYNG or from the underlying maternal condition.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



SAkuraStar: reduced relapse risk with ENSPRYNG monotherapy[1]

A randomized, double-blind, multicenter, placebo-controlled trial[1,10]

SAkuraStar study design[1,10]

Double-blind period*

AQP4-IgG(+) (n=64)
Randomized 2:1

- **ENSPRYNG** SC 120 mg Q4W (n=41)
- **Placebo** (n=23)

The double-blind period ended at 1.5 years after randomization of last patient

Key inclusion criteria[1,10]

- 95 adult patients (18 to 74 years) with NMO or NMOSD
  - 64 AQP4-IgG(+); 31 AQP4-IgG(-)
- ≥1 attack in the last year

Key exclusion criteria[1,10]

- Patients were excluded if they had taken ISTs within an interval specified for each such therapy

*Patients were randomized to receive ENSPRYNG 120 mg or placebo administered SC at Weeks 0, 2, and 4, and once every 4 weeks thereafter.[10]
ISTs=immunosuppressive therapies; Q4W=every 4 weeks; SC=subcutaneous.

Important Safety Information

Use in Specific Populations (cont'd)
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

Baseline characteristics in the SAkuraStar trial[45,46]

Participants in the trial reflected the real-world population of patients with NMOSD[10]

AQP4-IgG(+) patients	ENSPRYNG (n=41)	Placebo (n=23)
Age (mean)	46	40
Female (%)	76	96
NMOSD severity		
ARR in previous 2 years	0.91	1.02
EDSS (mean)	4.02	3.43

ARR=annualized relapse rate; EDSS=Expanded Disability Status Scale.



Important Safety Information

Use in Specific Populations (cont'd)

Geriatric Use

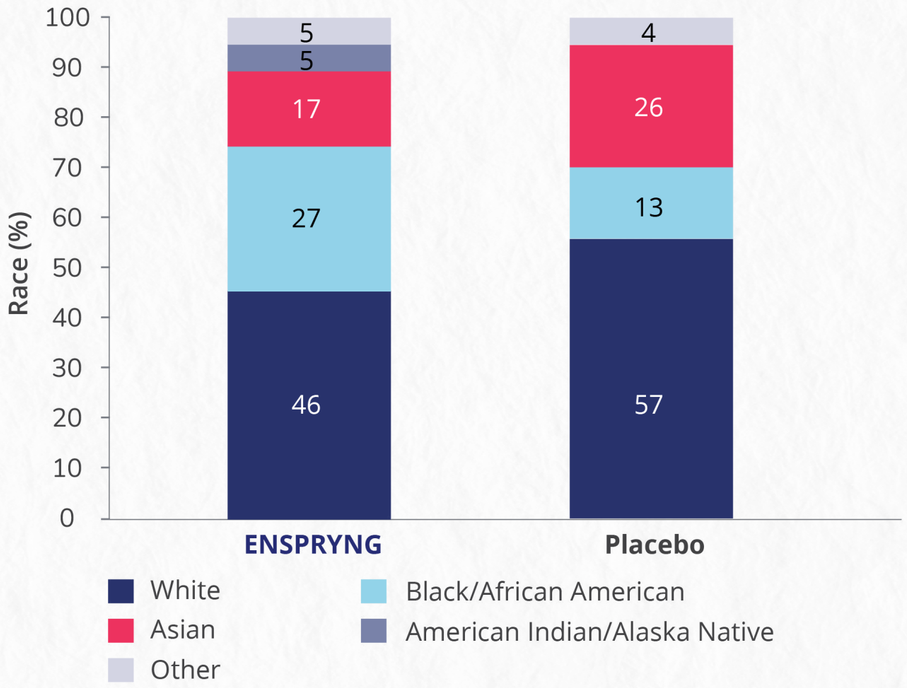
Clinical studies of ENSPRYNG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. However, population pharmacokinetic analyses in patients with NMOSD did not show that age affected the pharmacokinetics of ENSPRYNG. In general, caution should be used when dosing the elderly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

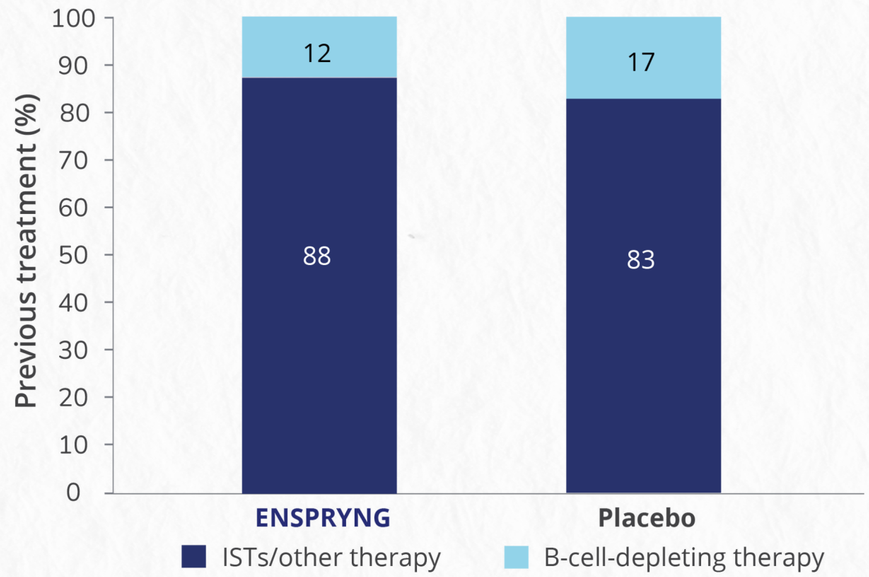
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☆ Baseline characteristics in the SAkuraStar trial (cont'd)[45,46]

SAkuraStar included a diverse population, encompassing patients who received prior ISTs or B-cell-depleting therapy





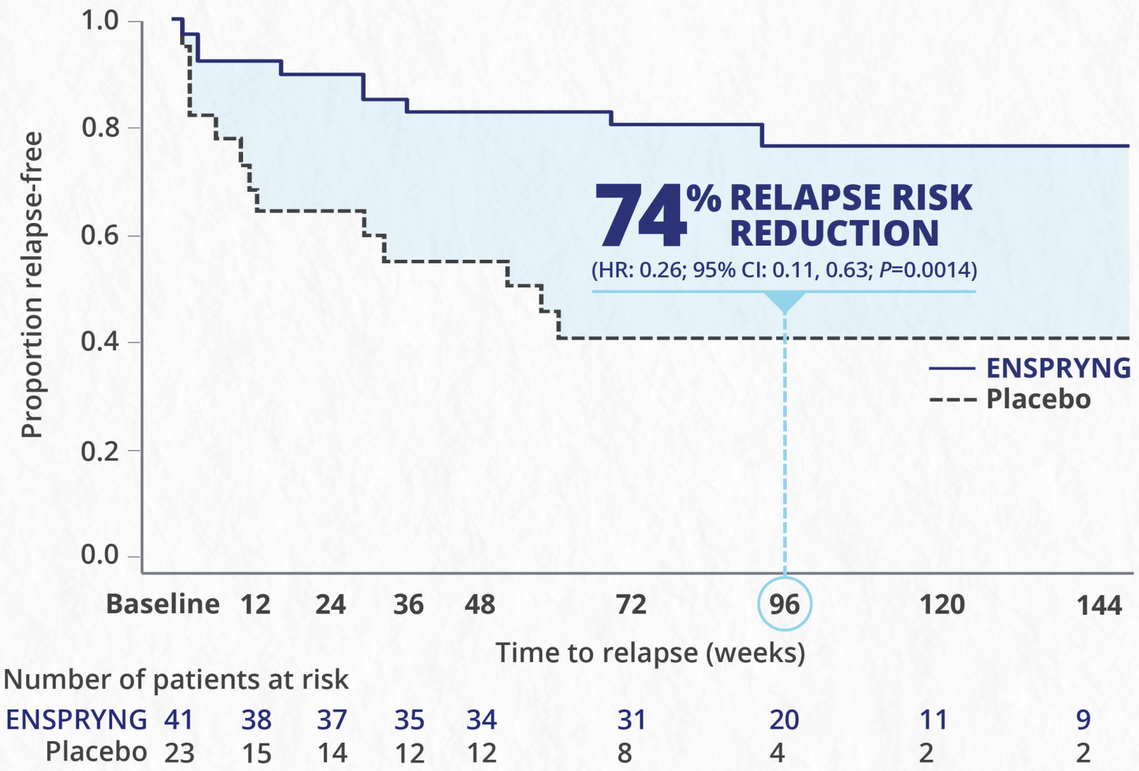
Important Safety Information

Most Common Adverse Reactions

The most common adverse reactions (≥15% in either trial) were nasopharyngitis (31%), headache (27%), upper respiratory tract infection (19%), rash (17%), arthralgia (17%), extremity pain (15%), gastritis (15%), fatigue (15%), and nausea (15%). You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

With ENSPRYNG, time to first relapse was longer in AQP4-IgG(+) patients[1]



CI=confidence interval; HR=hazard ratio.

Patients remained relapse-free at **nearly twice the rate** with ENSPRYNG vs placebo

8 out of 10
(77%) patients taking ENSPRYNG
WERE RELAPSE-FREE AT 96 WEEKS

vs

4 out of 10
(41%) patients taking placebo
WERE RELAPSE-FREE AT 96 WEEKS

"With ENSPRYNG I feel confident that the chance of a relapse is reduced. And that gives me peace of mind."
- Donna, ENSPRYNG patient since 2020

Important Safety Information

The warnings and precautions for ENSPRYNG are infections, including hepatitis B virus reactivation and tuberculosis, elevated liver enzymes, decreased neutrophil counts, and hypersensitivity reactions. Appropriate precautions should be taken by the healthcare provider when considering vaccinations.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



SAkuraSky: reduced relapse risk with ENSPRYNG + IST[1]

A randomized, double-blind, multicenter, placebo-controlled trial[1,43]

SAkuraSky study design[1,9]

Double-blind period*

Adults AQP4-IgG(+) (n=52)
Randomized 1:1

- **ENSPRYNG** SC 120 mg Q4W + **IST** (n=26)
- **Placebo + IST** (n=26)

The double-blind period ended when the total number of protocol-defined relapses reached 26

*Patients were randomized to receive ENSPRYNG 120 mg or placebo administered subcutaneously at Weeks 0, 2, and 4, and once every 4 weeks thereafter.[9]

Key inclusion criteria[1,9]

- 76 adult patients with NMO or NMOSD
  - 52 AQP4-IgG(+); 24 AQP4-IgG(-)
- ≥2 relapses in last 2 years (≥1 relapse in last year)
- Baseline treatment with a stable dose of IST, including azathioprine, mycophenolate mofetil, or oral corticosteroids, as monotherapy for 8 weeks prior to randomization

IST=immunosuppressive therapy; Q4W=every 4 weeks; SC=subcutaneous.

Important Safety Information

Contraindications

ENSPRYNG is contraindicated in patients with a known hypersensitivity to satralizumab or any of the inactive ingredients, an active hepatitis B infection, or active or untreated latent tuberculosis.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Baseline characteristics in the SAkuraSky trial[46]

AQP4-IgG(+) patients	ENSPRYNG + IST (n=26)	Placebo + IST (n=26)
Age (mean)	46	46
Female (%)	100	100
NMOSD severity		
ARR in previous 2 years	1.38	1.33
EDSS (mean)	4.21	3.72

ARR=annualized relapse rate; EDSS=Expanded Disability Status Scale.

Important Safety Information

Warnings and Precautions

Infections

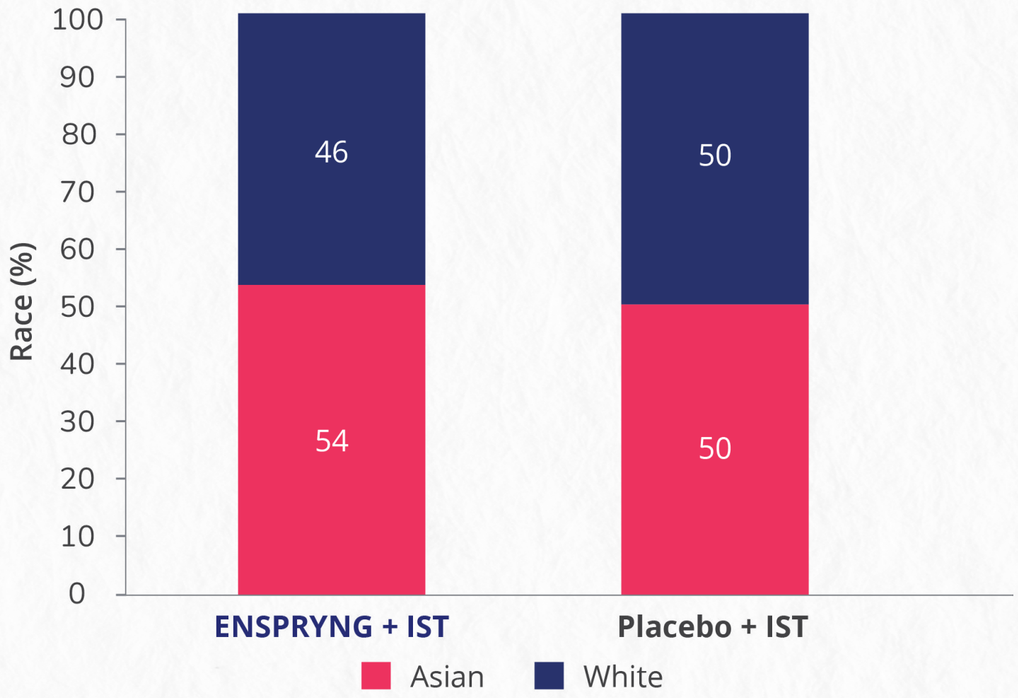
An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG. The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies, and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant, and that occurred more often than in patients receiving placebo, were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%). Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

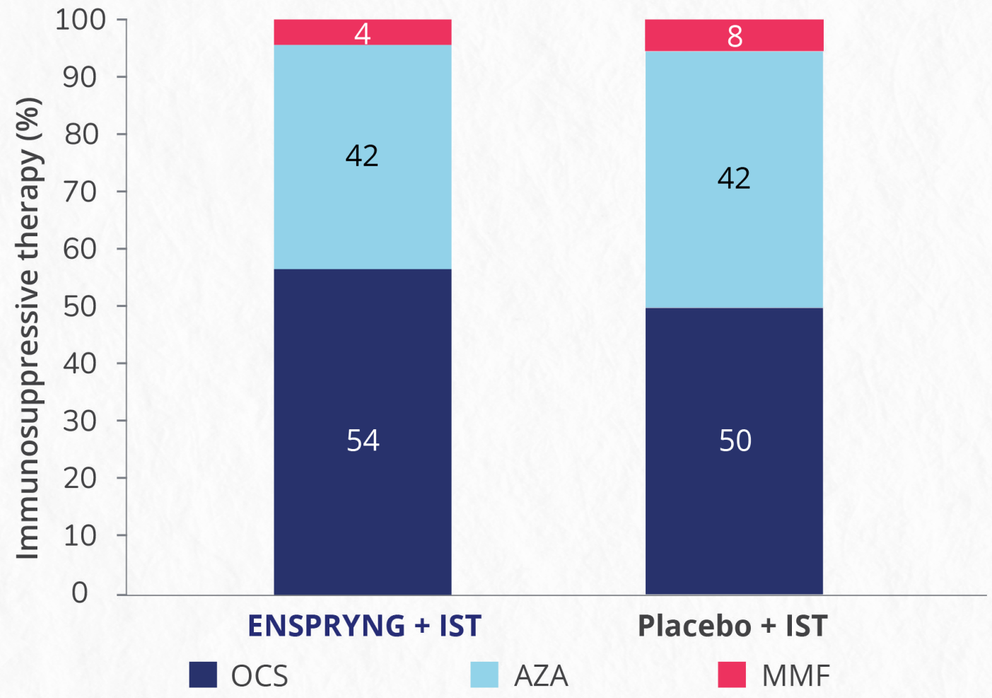
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Baseline characteristics in the SAkuraSky trial (cont'd)[46,47]

SAkuraSky included a large proportion of Asian patients and patients with a baseline treatment of IST





No patients had prior treatment with AZA or MMF in combination with OCS.

AZA=azathioprine; MMF=mycophenolate mofetil; OCS=oral corticosteroids.

Important Safety Information

Warnings and Precautions (cont'd)

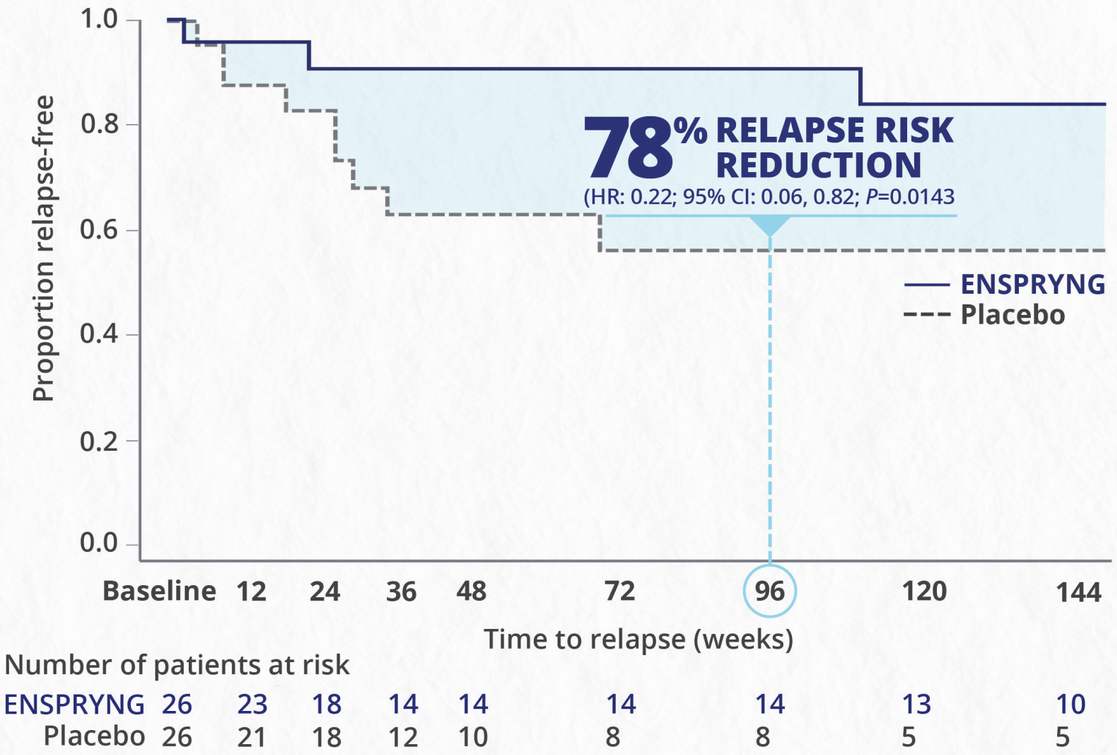
Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



ENSPRYNG + IST was shown to reduce relapse risk[1]



CI=confidence interval; HR=hazard ratio.

Majority of patients remained relapse-free with ENSPRYNG + IST

9 out of 10
(91%) patients taking ENSPRYNG
WERE RELAPSE-FREE AT 96 WEEKS

vs

6 out of 10
(57%) patients taking placebo
WERE RELAPSE-FREE AT 96 WEEKS

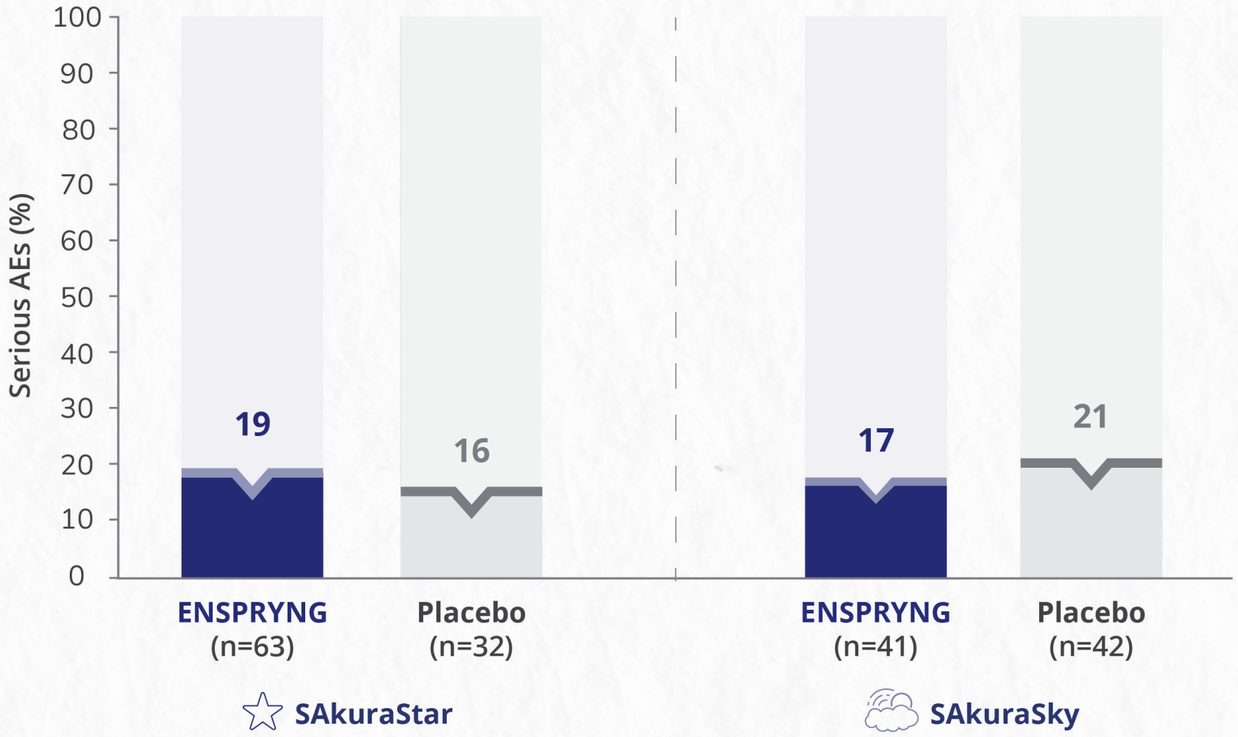
Important Safety Information

Warnings and Precautions (cont'd)

Tuberculosis
Tuberculosis has occurred in patients treated with other IL-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of signs and symptoms of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

Rates of serious AEs were comparable between ENSPRYNG and placebo in both clinical trials[4,9,10]*



"ENSPRYNG sounded like serious medicine, but NMOSD is a serious disease. After talking with my doctor, I felt comfortable moving forward."
- Cheena, ENSPRYNG patient since 2021

AEs=adverse events.
*The safety population included patients who received at least one dose of ENSPRYNG or placebo and included AQP4-seropositive and AQP4-seronegative patients.[9,10]

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



ENSPRYNG has a well-studied safety profile[5]

SAkuraStar: median ~2 years of safety data[1,48]*

Adverse reactions that occurred in ≥4 patients treated with ENSPRYNG	Patients (%)	
	ENSPRYNG (n=41)	Placebo (n=23)
Rash	17	0
Arthralgia	17	0
Pain in extremity	15	9
Fatigue	15	4
Nausea	15	9
Nasopharyngitis	12	4
Pruritus	10	0
Depression	10	0
Cellulitis	10	0
Neutropenia	10	4
Blood creatine phosphokinase increased	10	4
Fall	10	4

SAkuraSky: median ~3 years of safety data[1,48]*†

Adverse reactions that occurred in ≥3 patients treated with ENSPRYNG	Patients (%)	
	ENSPRYNG + IST (n=26)	Placebo + IST (n=26)
Nasopharyngitis	31	15
Headache	27	12
Upper respiratory tract infection	19	12
Gastritis	15	0
Arthralgia	12	0
Pharyngitis	12	8

*Patients receiving placebo were observed for a median of ~1 year.[1]
†All patients were concurrently receiving IST, which included oral corticosteroids, azathioprine, or mycophenolate mofetil.[1]
IST=immunosuppressive therapy.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



ENSPRYNG offers an established long-term safety profile, with a median exposure of 5 years[1,5]

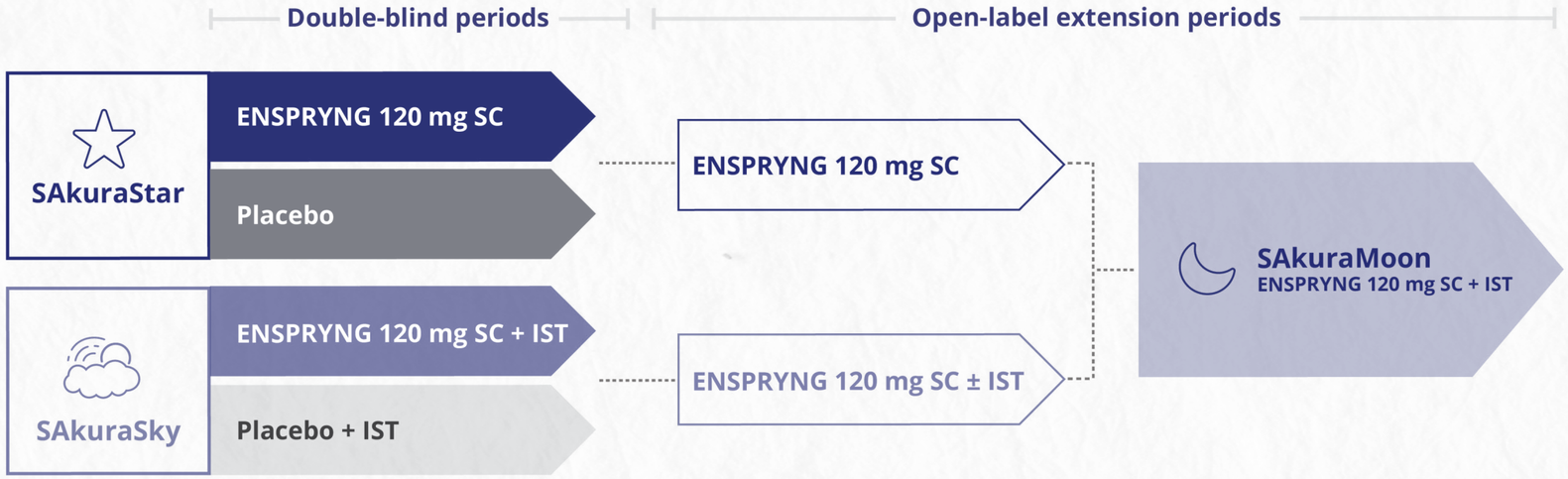
SAkuraMoon* included 106 patients who completed SAkuraStar and SAkuraSky

Patients from both studies entered the open-label extension period at CEC-confirmed relapse or at completion of the double-blind period.[†]

The overall ENSPRYNG treatment period was defined as follows:

- For ENSPRYNG-treated patients: double-blind + open-label extension periods
- For placebo patients: switched to ENSPRYNG at start of open-label extension periods

SAkuraMoon study design



- Safety assessments compared the rates of AEs per 100 patient-years in the overall vs the double-blind periods
- Median ENSPRYNG exposure was 5.0 (0.1-7.9) years

Limitations of the open-label, uncontrolled study period

- Patients in the open-label extension period successfully completed the controlled period and are subject to continued dropout; they may represent an enriched population. Conclusions regarding the safety of ENSPRYNG cannot be drawn on the basis of open-label extension data[49]

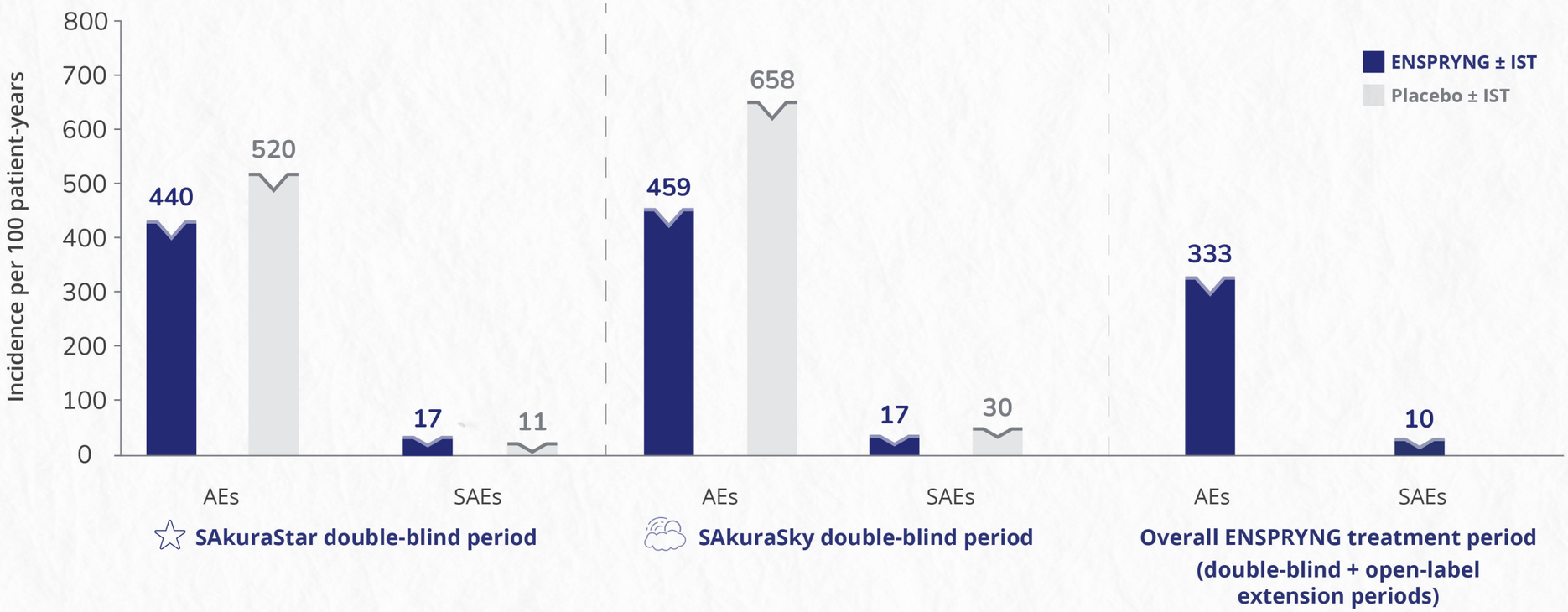
*SAkuraMoon is a single-arm, open-label study that enrolled patients who had completed the double-blind periods and open-label extensions of SAkuraSky and SAkuraStar.[5]
†CEC-confirmed PDR or clinical relapse requiring rescue therapy in SAkuraSky; CEC-confirmed PDR in SAkuraStar. Due to the COVID-19 pandemic, at-home dosing of ENSPRYNG was permitted from April 2020 onward.[5]
CEC=clinical endpoint committee; PDR=protocol-defined relapse; SC=subcutaneous.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Long-term safety of ENSPRYNG in AQP4-IgG(+) patients

The rates of AEs and serious AEs* for ENSPRYNG were similar in the double-blind and overall treatment periods[5]



- There were no deaths or anaphylactic reactions related to treatment with ENSPRYNG[1,5]
- All injection-related reactions were nonserious, and none led to treatment discontinuation or interruption[1,5†]
- Longer exposure to ENSPRYNG in the overall treatment period was not associated with a higher risk of severe (CTCAE grade ≥3) laboratory changes vs the double-blind periods[5]

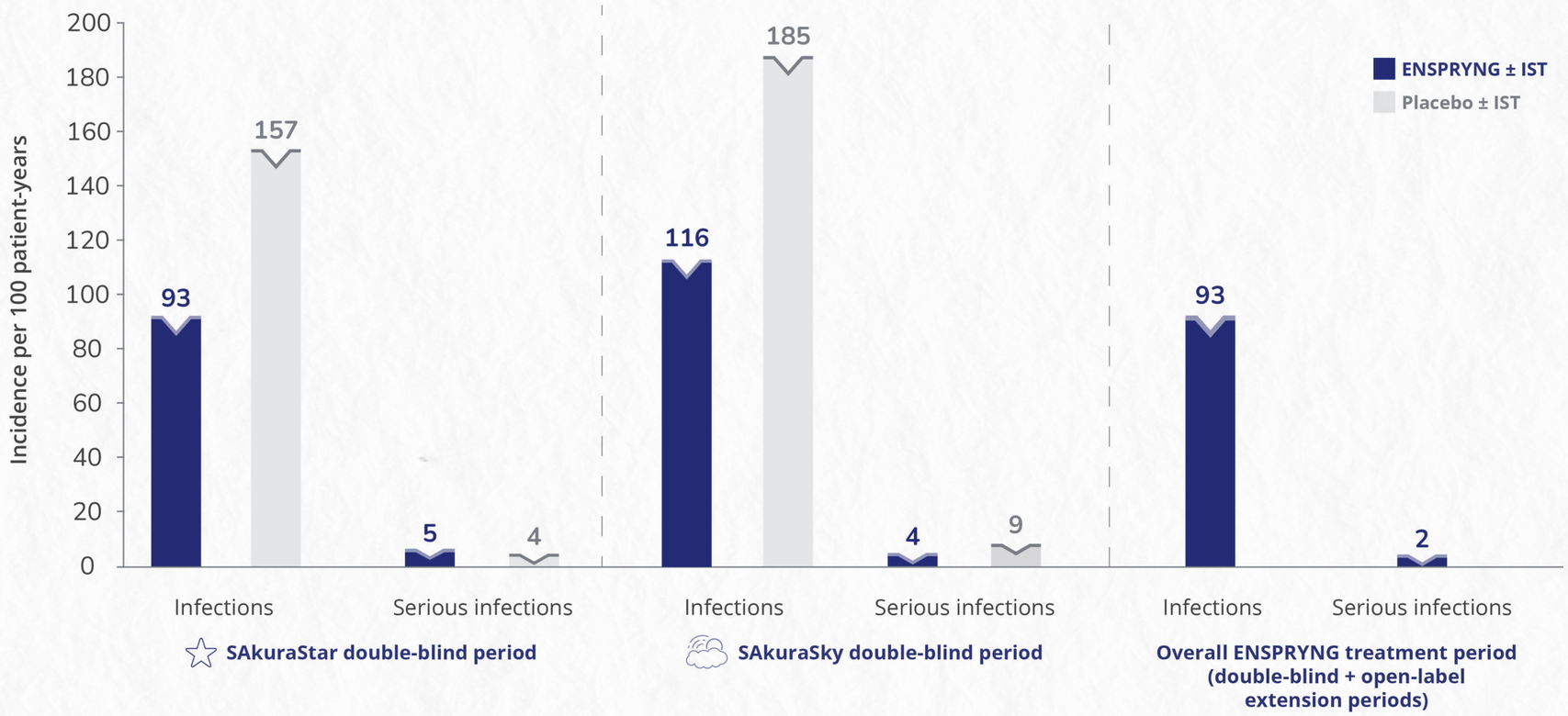
*The most common SAEs in the placebo ± IST for the SAkuraSky double-blind period were under the MedDRA system organ classes: blood and lymphatic disorders, and infections and infestations.[5]
†SAEs are any AEs that are fatal, life threatening, require hospitalization, result in disability or incapacity, cause congenital anomalies or birth defects, and/or are judged by investigators to be significant medical events.[5]
CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; SAEs=serious adverse events.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Long-term safety of ENSPRYNG in AQP4-IgG(+) patients (cont'd)

The rates of infections and serious infections* for ENSPRYNG were similar in the double-blind and overall treatment periods[5]



- In both periods, the most common infections with ENSPRYNG were upper respiratory tract infections and urinary tract infections

*MedDRA system organ class: infections and infestations.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

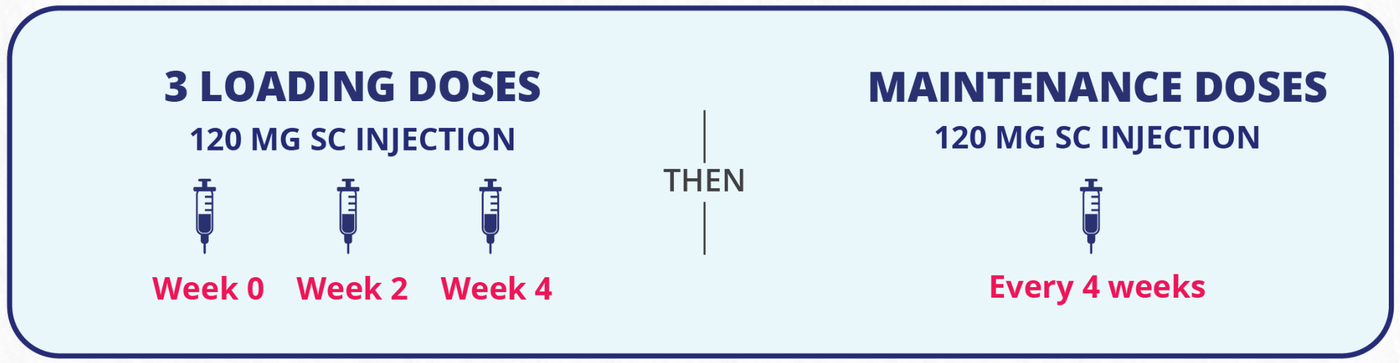
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satralizumab-mwge
subcutaneous injection 120 mg/mL



Offer the flexibility of the only monthly subcutaneous NMOSD treatment[1,29,31,32,50]

Patients can self-inject ENSPRYNG after proper training[1,32]

ENSPRYNG is intended to be self-administered under the guidance of a healthcare provider. After proper training and approval from a healthcare provider, your patients can self-administer treatment with ENSPRYNG.



- At initiation, a loading dose of ENSPRYNG 120 mg is administered by SC injection every other week for a total of 3 injections[1]
- Maintenance doses are administered thereafter at an interval of once every 4 weeks[1]

ENSPRYNG storage and handling[1]

- Refrigerate at 36°F to 46°F (2°C to 8°C) before administration
- ENSPRYNG can remain stable at room temperature (not to exceed 86°F/30°C) for up to 8 days, allowing patients to administer at home or on the go

SC=subcutaneous.

Important Safety Information

Warnings and Precautions (cont'd)

Vaccinations
Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

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Patient monitoring prior to and during ENSPRYNG treatment[1]

Assessments prior to the first dose of ENSPRYNG

- **HBV screening:** ENSPRYNG should not be initiated in patients with active HBV
- **Tuberculosis screening:** evaluate for active tuberculosis and test for latent infection
- **Liver transaminase screening:** liver transaminases and serum bilirubin should be assessed prior to initiation of treatment
- **Vaccination:** administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior for non-live vaccines

Patient monitoring during ENSPRYNG treatment

- **Liver transaminases:** monitor ALT and AST levels every 4 weeks for the first 3 months of treatment, followed by every 3 months for 1 year, and thereafter as clinically necessary
- **Neutrophil counts:** monitor neutrophils 4 to 8 weeks after initiation of therapy and thereafter at regular clinically determined intervals

Monitoring schedule: patient's first year on ENSPRYNG

WEEKS	0*	4	8	12	16	20	24	28	32	36	40	44	48	52
ALT and AST†		✓	✓	✓			✓			✓			✓	
Neutrophils		✓												

*Time of first administration.
†Liver transaminases should be assessed prior to initiation of ENSPRYNG.
ALT=alanine aminotransferase; AST=aspartate transaminase; HBV=hepatitis B virus.

Important Safety Information

Warnings and Precautions (cont'd)

Elevated Liver Enzymes
Mild and moderate elevations of liver enzymes have been observed in patients treated with ENSPRYNG at a higher incidence than in patients receiving placebo. ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for one year, and thereafter, as clinically indicated.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

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Managing changes in liver transaminases during ENSPRYNG treatment[1]

Dose management

If ALT or AST levels exceed 5x the ULN, discontinue ENSPRYNG as follows:

- **if any bilirubin elevation is detected:** discontinue ENSPRYNG; reinitiation is not recommended
- **if bilirubin is normal:** when ALT or AST return to normal and a benefit-risk assessment is performed, restart treatment per schedule below
  - Upon restarting treatment, closely monitor liver parameters. Discontinue and do not restart ENSPRYNG if ALT, AST, or bilirubin rise above the ULN

Clinical trial experience

- **SAkuraStar:** ALT and AST levels rose above the ULN in 43% and 25% of patients taking ENSPRYNG, respectively, vs 13% and 9% with placebo
- **SAkuraSky:** ALT and AST levels rose above the ULN in 8% and 8% of patients taking ENSPRYNG, respectively, vs 12% and 19% with placebo
- **SAkuraStar and SAkuraSky**: 3% of patients in ENSPRYNG group experienced ALT or AST elevations over 3X the ULN (vs none in placebo group)*

Last dose administered	Recommended dosage for restart of treatment after liver transaminase elevation
<12 weeks	Restart at a dosage of 120 mg by SC every 4 weeks
12 weeks or longer	Restart at a dose of 120 mg by SC at Weeks 0,† 2, and 4, followed by a dosage of 120 mg every 4 weeks

*These elevations were not associated with increases in total bilirubin. One patient in SAkuraSky had ALT levels rise above 5X the ULN, which was observed 4 weeks after initiation of therapy, normalizing 78 days after discontinuation of ENSPRYNG.
†"0 weeks" refers to time of the first administration after the missed dose.
ULN=upper limit of normal.

Important Safety Information

Warnings and Precautions (cont'd)

Decreased Neutrophil Counts
Decreases in neutrophil counts were observed in patients treated with ENSPRYNG at a higher incidence than placebo. Neutrophil counts should be monitored 4 to 8 weeks after initiation of therapy, and thereafter at regular clinically determined intervals.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Managing changes in neutrophil count during ENSPRYNG treatment[1]

Dose management

- **If neutrophil count is below 1.0 x 10^9/L and confirmed by repeat testing, ENSPRYNG should be interrupted**
- **Resume treatment** once neutrophil count is >1.0 X 10^9/L

Clinical trial experience

- **SAkuraStar:** 10% of patients taking ENSPRYNG had neutrophils below 1 x 10^9/L vs 9% with placebo*
- **SAkuraSky:** 15% of patients taking ENSPRYNG had neutrophils below 1 x 10^9/L vs 4% with placebo†

*There was one patient in SAkuraStar treated with ENSPRYNG with neutrophil counts <0.5 x 10^9/L.
†One patient in SAkuraSky discontinued ENSPRYNG because of neutropenia.

If a dose of ENSPRYNG is missed for any reason other than increases in liver enzymes, refer to the table below.

Time since last dose	Recommended dosage for delayed or missed doses
<8 weeks during the maintenance period or missed a loading dose	Administer 120 mg by SC injection as soon as possible, and do not wait until the next planned dose. **Maintenance period** • After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks **Loading period** • If the second loading dose is delayed or missed, administer as soon as possible and administer the third and final loading dose 2 weeks later • If the third loading dose is delayed or missed, administer as soon as possible and administer the first maintenance dose 4 weeks later
8 weeks to <12 weeks	**120 mg by SC injection at 0‡ and 2 weeks, followed by 120 mg every 4 weeks**
≥12 weeks	**120 mg by SC injection at 0,‡ 2, and 4 weeks, followed by 120 mg every 4 weeks**

‡"0 weeks" refers to time of the first administration after the missed dose.

Important Safety Information

Warnings and Precautions (cont'd)

Hypersensitivity Reactions
Hypersensitivity reactions, including rash, urticaria, and fatal anaphylaxis, have occurred with other IL-6 receptor antagonists.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Genentech is here to support starting your patients on ENSPRYNG as quickly as possible

No additional vaccines required before starting treatment[1]

Beyond routine vaccinations, no additional vaccines are required before starting ENSPRYNG.*

Monthly at-home self-administration after training[1]

After proper training by a healthcare provider, patients can start self-administering ENSPRYNG at home or on the go.

Majority of patients covered

~75% of commercial patients nationwide have unrestricted first-line coverage for ENSPRYNG—no need for patient to fail other therapies.[51†]

Free sample doses for your practice

The ENSPRYNG sample program provides the first 2 months of treatment (3 loading doses and the first maintenance dose).[1‡§] This program is designed to help you become familiar with ENSPRYNG by building experience for you and your eligible patients with NMOSD, and to determine whether self-administration is appropriate.

Learn more and submit sample requests with your local Genentech representative, or call the Sample Accountability Call Center at 1-866-736-2717 (Monday through Friday, 8 AM to 6 PM ET)

*According to immunization guidelines, all immunizations should be administered at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, wherever possible, at least 2 weeks prior for non-live vaccines.[1]

†Because drug coverage policies can change, please check with the health plan directly to confirm coverage for individual patients. Coverage policies current as of November 2024.

‡Drug samples may not be sold, purchased, traded, or offered for sale, purchase, or trade, utilized to seek reimbursement, or otherwise distributed in a manner not permitted by applicable law. Samples may only be distributed to practitioners who are licensed or authorized under applicable law to prescribe the drug product and whose practices are relevant to the FDA-approved product labeling for ENSPRYNG. Distribution of the sample does not obligate use or continuing use of ENSPRYNG. You may not advertise or otherwise use the program as a means of promoting your services or Genentech products to patients. Genentech reserves the right to deny fulfillment of the sample to anyone deemed ineligible in accordance with stated program criteria.

§Annual sample limits per healthcare provider apply.

Important Safety Information

Use in Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENSPRYNG during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-277-9338.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Access support for your patients

At Genentech, we know it is a privilege to help patients. We are dedicated to helping ensure our medicines are accessible for the patients who have been prescribed them.

Genentech Access Solutions can help your patients:

- Better understand their coverage
- Find financial assistance options
- Learn how to get the Genentech medicine they have been prescribed
- Understand which SP their health insurance plan requires
- Reverify coverage if needed
- Enroll in additional support options in the event of a coverage delay

If a plan issues a denial, the denial should be reviewed, along with the health insurance plan's guidelines, to determine what to include in your patient's appeal submission. Your Genentech reimbursement representative or Genentech Access Solutions Specialist has local payer coverage expertise and can help you determine specific requirements for your patient.

Genentech offers assistance for patients with different types of insurance coverage:

- Commercially insured patients may be able to use a Genentech co-pay program or be referred to an independent co-pay assistance foundation
- Publicly insured patients can be referred to independent co-pay assistance foundations
- Eligible patients with or without insurance coverage may receive help from the Genentech Patient Foundation

Visit enspryng-hcp.com for more information about access support for your patients.

SP=specialty pharmacy.

Important Safety Information

Use in Specific Populations (cont'd)

Pregnancy
Pregnancy Exposure Registry
There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of ENSPRYNG at doses up to 50 mg/kg/week. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

ENSPRYNG®
satralizumab-mwge
subcutaneous injection 120 mg/mL

Individualized support for your patients

We understand that every patient's needs are unique, and we help you get the support you need to address your individual concerns

Patient Navigators

Your Patient Navigator is a point of contact for assistance throughout your patients' treatment, including access, reimbursement and infusion coordination support.

Your Patient Navigator can:

- Facilitate enrollment in Genentech Access Solutions
- Address patient-specific access questions
- Conduct BIs and offer support for PAs
- Identify an appropriate SP and follow up with the SP regarding fulfillment status
- Connect patients to appropriate financial assistance options
- Locate an infusion site and coordinate the infusion
- Educate patients about clinical injection training support

Clinical Education Managers (CEMs)*

ENSPRYNG CEMs can provide personal support to patients prescribed ENSPRYNG and their caregivers from day one—all at no cost. After receiving initial training from their healthcare provider, patients can access resources to reinforce what they've learned. CEMs do not perform injections.

CEMs can provide your patients:

- In-person or virtual educational sessions
- Resources and information about NMOSD
- 1:1 support from our dedicated team of experts
- Supplemental injection training support

Encourage your patients to schedule their first session with a CEM by calling **1-844-NSPRYNG** or visiting **enspryng.com/CEM**.

*This program is intended primarily for patients prescribed ENSPRYNG who are in their first year of treatment. CEMs are Genentech employees and do not provide medical advice.

BIs=benefit investigations; PAs=prior authorizations.

Important Safety Information

Use in Specific Populations (cont'd)

Lactation

No information is available on the presence of ENSPRYNG in human milk, the effects of ENSPRYNG on the breastfed infant, or the effects of ENSPRYNG on milk production. ENSPRYNG was excreted in the milk of lactating monkeys administered ENSPRYNG throughout pregnancy. Human IgG is excreted in human milk and the potential for absorption in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and any potential adverse effects on the breastfed infant from ENSPRYNG or from the underlying maternal condition.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Meet Garcelle[1]* | 35 years | Newly diagnosed

Have you seen patients like her in your practice?

Garcelle works full-time and cares for her 2 children.

*Not a real patient.

Select medical history

- Initially misdiagnosed with MS and began MS treatment 8 months ago; symptoms did not fully resolve[2]
- Had an attack 2 months ago and was given high-dose IV steroids
- Tested positive for AQP4 antibodies, confirming the diagnosis of AQP4-IgG(+) NMOSD

Clinical presentation

- Experiences partial vision loss, has numbness and weakness in her legs[2]
- EDSS score 4.0

Patient goal

- Wants to get on a treatment as soon as possible to control her symptoms but doesn't want it to get in the way of her busy lifestyle

Choose ENSPRYNG for your appropriate adult patients with AQP4-IgG(+) NMOSD[1]

EDSS=Expanded Disability Status Scale; IV=intravenous; MS=multiple sclerosis.

Important Safety Information

Use in Specific Populations (cont'd)

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Meet Lucy[1]* | 42 years | On IST monotherapy

Have you seen patients like her in your practice?

Lucy works full-time and lives in a rural area.

*Not a real patient.

Select medical history

- Diagnosed with AQP4-IgG(+) NMOSD 2 years ago
- Had an acute attack within the past year, recovered almost fully, but not completely back to baseline
- Currently taking azathioprine

Patient goal

- Concerned her current treatment alone isn't enough to prevent a future NMOSD relapse

Clinical presentation

- In the past month, she's had moderate blurred vision in her left eye, tingling sensations in her lower limbs, and has lost her balance a few times. She reported no new weakness or pain[2]
- EDSS score 4.5

Choose ENSPRYNG for your appropriate adult patients with AQP4-IgG(+) NMOSD[1]

EDSS=Expanded Disability Status Scale; IST=immunosuppressive therapy.

Important Safety Information

Use in Specific Populations (cont'd)

Geriatric Use
Clinical studies of ENSPRYNG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. However, population pharmacokinetic analyses in patients with NMOSD did not show that age affected the pharmacokinetics of ENSPRYNG. In general, caution should be used when dosing the elderly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.



Meet Sarah[1]* | 46 years | On a biologic therapy

Have you seen patients like her in your practice?

Sarah works part-time and loves to travel.

*Not a real patient.

Select medical history

- Diagnosed with AQP4-IgG(+) NMOSD 10 years ago
- Previous relapse of optic neuritis and transverse myelitis in the last year
- Currently taking an anti-CD20 monoclonal antibody for maintenance therapy[46]
- Has diabetes[45]

Clinical presentation

- She is still fully ambulatory, but she sometimes experiences bladder and bowel dysfunction[2]
- Experiences recurrent urinary tract infections[2]
- EDSS score 3.5

EDSS=Expanded Disability Status Scale.

Patient goal

- Worried about continued infections impacting her life over the long term and wants to find another solution[4,5]

Choose ENSPRYNG for your appropriate adult patients with AQP4-IgG(+) NMOSD[1]

Important Safety Information

Most Common Adverse Reactions
The most common adverse reactions (≥15% in either trial) were nasopharyngitis (31%), headache (27%), upper respiratory tract infection (19%), rash (17%), arthralgia (17%), extremity pain (15%), gastritis (15%), fatigue (15%), and nausea (15%). You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

ENSPRYNG®
satralizumab-mwge
subcutaneous injection 120 mg/mL

Celebrate ordinary moments for your AQP4-IgG(+) NMOSD patients with ENSPRYNG

ENSPRYNG modulates the immune response by blocking the IL-6 receptor to treat NMOSD without directly affecting the innate immune system in the same way that broader immunosuppressants do.[1,37-39]

Only ENSPRYNG reduced the risk of relapse in two distinct phase 3 clinical trials and offers an established long-term safety profile, with a median exposure of 5 years.[1,9,10,29,31,32,50]

Beyond routine vaccinations, no additional vaccines are required before starting ENSPRYNG.* After proper training by a healthcare provider, patients can start **self-administering ENSPRYNG** at home or on the go.[1]

The Neuromyelitis Optica Study Group (NEMOS) 2024 Guidelines recommend ENSPRYNG as a **first-line treatment option** for NMOSD.[25]

Since approval, **5500+ patients have been treated globally with ENSPRYNG**.[44†]



*According to immunization guidelines, all immunizations should be administered at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, wherever possible, at least 2 weeks prior for non-live vaccines.[1]
†Based on individuals with AQP4-IgG(+) NMOSD receiving ENSPRYNG worldwide as of May 2024.[44]

IL-6=interleukin-6.

Important Safety Information

Most Common Adverse Reactions
The warnings and precautions for ENSPRYNG are infections, including hepatitis B virus reactivation and tuberculosis, elevated liver enzymes, decreased neutrophil counts, and hypersensitivity reactions. Appropriate precautions should be taken by the healthcare provider when considering vaccinations.

Please see additional Important Safety Information throughout this piece, and click here for full Prescribing Information and Medication Guide.

ENSPRYNG®
satralizumab-mwge
subcutaneous injection 120 mg/mL

Important Safety Information

Indication

ENSPRYNG is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Contraindications

ENSPRYNG is contraindicated in patients with a known hypersensitivity to satralizumab or any of the inactive ingredients, an active hepatitis B infection, or active or untreated latent tuberculosis.

Warnings and Precautions

Infections

An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG. The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies, and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant, and that occurred more often than in patients receiving placebo, were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%). Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

Tuberculosis

Tuberculosis has occurred in patients treated with other IL-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of signs and symptoms of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

Vaccinations

Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

Elevated Liver Enzymes

Mild and moderate elevations of liver enzymes have been observed in patients treated with ENSPRYNG at a higher incidence than in patients receiving placebo. ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for one year, and thereafter, as clinically indicated.

Decreased Neutrophil Counts

Decreases in neutrophil counts were observed in patients treated with ENSPRYNG at a higher incidence than placebo. Neutrophil counts should be monitored 4 to 8 weeks after initiation of therapy, and thereafter at regular clinically determined intervals.

Hypersensitivity Reactions

Hypersensitivity reactions, including rash, urticaria, and fatal anaphylaxis, have occurred with other IL-6 receptor antagonists.

Important Safety Information (cont'd)

Use in Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENSPRYNG during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-277-9338.

There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of ENSPRYNG at doses up to 50 mg/kg/week. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

No information is available on the presence of ENSPRYNG in human milk, the effects of ENSPRYNG on the breastfed infant, or the effects of ENSPRYNG on milk production. ENSPRYNG was excreted in the milk of lactating monkeys administered ENSPRYNG throughout pregnancy. Human IgG is excreted in human milk and the potential for absorption in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and any potential adverse effects on the breastfed infant from ENSPRYNG or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of ENSPRYNG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. However, population pharmacokinetic analyses in patients with NMOSD did not show that age affected the pharmacokinetics of ENSPRYNG. In general, caution should be used when dosing the elderly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

Most Common Adverse Reactions

The most common adverse reactions (≥15% in either trial) were nasopharyngitis (31%), headache (27%), upper respiratory tract infection (19%), rash (17%), arthralgia (17%), extremity pain (15%), gastritis (15%), fatigue (15%), and nausea (15%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

For additional safety information, please see the full Prescribing Information and Medication Guide.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENSPRYNG safely and effectively. See full prescribing information for ENSPRYNG.

ENSPRYNG® (satralizumab-mwge) injection, for subcutaneous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

ENSPRYNG is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, tuberculosis, and liver transaminase screening is required before the first dose. (2.1)
- Prior to every use, determine if there is an active infection. (2.2)
- The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks. (2.2)
- See Full Prescribing Information for important preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Known hypersensitivity to satralizumab or any of the inactive ingredients (4)
- Active Hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infections: Delay ENSPRYNG administration in patients with an active infection until the infection is resolved. Vaccination with live or live-attenuated vaccines is not recommended during treatment. (5.1)
- Elevated Liver Enzymes: Monitor ALT and AST levels during treatment; interruption of ENSPRYNG may be required. (5.2)
- Decreased Neutrophil Counts: Monitor neutrophils during treatment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 15%) are nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENSPRYNG is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to the First Dose of ENSPRYNG

Hepatitis B Virus Screening

Prior to initiating ENSPRYNG, perform Hepatitis B virus (HBV) screening. ENSPRYNG is contraindicated in patients with active HBV confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with ENSPRYNG *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Tuberculosis Screening

Prior to initiating ENSPRYNG, evaluate for active tuberculosis and test for latent infection. For patients with active tuberculosis or positive tuberculosis screening without a history of appropriate treatment, consult infectious disease experts before initiating treatment with ENSPRYNG *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Liver Transaminase Screening

Liver transaminases and serum bilirubin should be assessed prior to initiation of treatment with ENSPRYNG *[see Warnings and Precautions (5.2)]*.

Caution should be exercised when considering initiation of ENSPRYNG treatment in patients whose aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels are greater than 1.5 times the upper limit of normal (ULN).

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment with ENSPRYNG, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines *[see Warnings and Precautions (5.1).*

2.2 Recommended Dosage

For subcutaneous use only.

Prior to every use of ENSPRYNG, advise patients to consult with their healthcare professional (HCP) if they suspect an active infection, including localized infections. In case of active infection, delay use of ENSPRYNG until the infection is resolved *[see Warnings and Precautions (5.1)]*.

The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks.

Missed Dose

If a dose of ENSPRYNG is missed for any reason other than increases in liver enzymes *[see Dosage and Administration (2.4)]*, administer as described in Table 1.

Table 1 Recommended Dosage for Delayed or Missed Doses

Last Dose Administered	Recommended Dosage for Delayed or Missed Doses
Less than 8 weeks during the maintenance period or missed a loading dose	Administer 120 mg by subcutaneous injection as soon as possible, and do not wait until the next planned dose. Maintenance period After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks. Loading period If the second loading dose is delayed or missed, administer as soon as possible and administer the 3rd and final loading dose 2 weeks later. If the third loading dose is delayed or missed, administer as soon as possible and administer the 1st maintenance dose 4 weeks later.
8 weeks to less than 12 weeks	120 mg by subcutaneous injection at 0* and 2 weeks, followed by 120 mg every 4 weeks.
12 weeks or longer	120 mg by subcutaneous injection at 0*, 2, and 4 weeks followed by 120 mg every 4 weeks.

* "0 weeks" refers to time of the first administration after the missed dose.

2.3 Important Administration Instructions

- ENSPRYNG is intended for patient self-administration by subcutaneous injection under the guidance of a health care professional (HCP). After proper training in subcutaneous injection technique, a patient may self-inject ENSPRYNG or the patient's caregiver may administer ENSPRYNG, if the HCP determines that it is appropriate. See ENSPRYNG "Instructions for Use" (IFU) for more detailed instructions on the preparation and administration of ENSPRYNG.
- Patients or caregivers should seek immediate medical attention if the patient develops symptoms of a serious allergic reaction and should not administer further doses until evaluated by a HCP *[see Contraindications (4) and Warning and Precautions (5.4)]*.
- Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes. Do not warm ENSPRYNG in any other way.
- Inspect visually for particulate matter and discoloration prior to administration. ENSPRYNG solution should be clear and colorless to slightly yellow. Do not use ENSPRYNG if the solution is cloudy, discolored, or contains particles, or if any part of the prefilled syringe appears to be damaged.
- Instruct patients to inject the full amount in the syringe (1 mL), which provides 120 mg of ENSPRYNG, according to the directions provided in the IFU.
- Administer ENSPRYNG by subcutaneous injection in the abdomen or thigh. Rotate injection sites with each administration. Do not give injection into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

2.4 Safety Monitoring During Treatment

Liver Transaminases

Monitor ALT and AST levels every 4 weeks for the first 3 months of treatment with ENSPRYNG, followed by every 3 months for one year, and thereafter as clinically necessary *[see Warnings and Precautions (5.2)]*.

If an ALT or AST elevation of greater than 5 times the ULN occurs, discontinue ENSPRYNG as follows:

- If associated with any bilirubin elevation, discontinue ENSPRYNG, and reinitiation is not recommended.
- If not associated with any bilirubin elevation above the ULN, when the ALT or AST level has returned to the normal range and following a benefit-risk assessment of the patient, treatment with ENSPRYNG can be restarted per the schedule in Table 2.

Table 2 Recommended Dosage for Restart of Treatment After Liver Transaminase Elevation

Last Dose Administered	Recommended Dosage for Restart of Treatment
Less than 12 weeks	Restart at a dosage of 120 mg by subcutaneous injection every 4 weeks.
12 weeks or longer	Restart at a dose of 120 mg by subcutaneous injection at Weeks 0*, 2, and 4, followed by a dosage of 120 mg every 4 weeks.

* "0 weeks" refers to time of the first administration after the missed dose.

If treatment is restarted, the liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin above the ULN is observed, ENSPRYNG should be discontinued, and another reinitiation is not recommended.

Neutrophil Counts

Monitor neutrophils 4 to 8 weeks after initiation of therapy and thereafter at regular clinically determined intervals. If the neutrophil count is below 1.0×10^9/L and confirmed by repeat testing, ENSPRYNG should be interrupted until the neutrophil count is > 1.0×10^9/L *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL clear, and colorless to slightly yellow solution in single-dose prefilled syringe.

4 CONTRAINDICATIONS

ENSPRYNG is contraindicated in patients with:

- A known hypersensitivity to satralizumab or any of the inactive ingredients *[see Warnings and Precautions (5.4)]*
- Active Hepatitis B infection *[see Warnings and Precautions (5.1)]*
- Active or untreated latent tuberculosis *[see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infections

An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG.

The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies (Study 1), and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant, and that occurred more often than in patients receiving placebo, were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%).

Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

Tuberculosis

Tuberculosis has occurred in patients treated with other interleukin-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of symptoms and signs of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

Vaccinations

Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

5.2 Elevated Liver Enzymes

Mild and moderate elevations of liver enzymes have been observed in patients treated with ENSPRYNG at a higher incidence than in patients receiving placebo *[see Adverse Reactions (6.1)]*.

ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for one year, and thereafter, as clinically indicated *[see Dosage and Administration (2.4)]*.

5.3 Decreased Neutrophil Counts

Decreases in neutrophil counts were observed in patients treated with ENSPRYNG at a higher incidence than placebo *[see Adverse Reactions (6.1)]*.

Neutrophil counts should be monitored 4 to 8 weeks after initiation of therapy, and thereafter at regular clinically determined intervals *[see Dosage and Administration (2.4)]*.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, urticaria, and fatal anaphylaxis, have occurred with other interleukin-6 receptor antagonists.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Elevated Liver Enzymes *[see Warnings and Precautions (5.2)]*
- Decreased Neutrophil Counts *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The safety of ENSPRYNG was evaluated in two randomized, placebo-controlled clinical trials [Study 1 evaluated ENSPRYNG without concurrent immunosuppressive therapy (IST) and Study 2 evaluated ENSPRYNG with concurrent IST], which included 41 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 1 and 26 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 2 *[see Clinical Studies (14)]*. In the double-blind, controlled period, the median exposure time on ENSPRYNG treatment was approximately 2 years in Study 1 and approximately 3 years in Study 2. The median exposure time on placebo treatment was approximately 1 year in both Study 1 and Study 2.

Adverse reactions that occurred in Study 1 and Study 2 in more than 5% of patients treated with ENSPRYNG, and at a greater incidence than in patients who received placebo, are shown in Table 3 and Table 4, respectively. The most common adverse reactions (15% or greater with ENSPRYNG in either) were nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea.

Table 3 Adverse Reactions Occurring in 4 or More Patients Treated with ENSPRYNG and Greater Incidence than Placebo in Study 1

Adverse Reaction	ENSPRYNG (N = 41) %	PLACEBO (N = 23) %
Rash	17	0
Arthralgia	17	0
Pain in extremity	15	9
Fatigue	15	4
Nausea	15	9
Nasopharyngitis	12	4
Pruritus	10	0
Depression	10	0
Cellulitis	10	0
Neutropenia	10	4
Blood creatine phosphokinase increased	10	4
Fall	10	4

Table 4 Adverse Reactions Occurring in 3 or More Patients Treated with ENSPRYNG and Greater Incidence than Placebo in Study 2

Adverse Reaction	ENSPRYNG + IST (N = 26) %	PLACEBO + IST (N = 26) %
Nasopharyngitis	31	15
Headache	27	12
Upper respiratory tract infection	19	12
Gastritis	15	0
Arthralgia	12	0
Pharyngitis	12	8

Injection-Related Reactions

In Study 1 and Study 2, injection-related reactions were reported in 9% of patients treated with ENSPRYNG compared with 8% in patients receiving placebo. These reactions in the ENSPRYNG-treated patients were predominantly mild to moderate in severity, and most occurred within 24 hours after the injection. The most commonly reported systemic symptom was diarrhea. The reported local injection site reactions were pruritus, injection site reaction, and skin mass.

Infections

In Study 1, the rate of patients with infections was 51 patients/100 patient-years (95% CI: 32, 78) in patients treated with ENSPRYNG compared with 108 patients/100 patient-years (95% CI: 52, 199) in patients receiving placebo. The rate of patients with serious infections was 5 patients/100 patient-years (95% CI: 1, 14) in patients treated with ENSPRYNG compared with 4 patients/100 patient-years (95% CI: 0, 21) in patients receiving placebo.

In Study 2, the rate of patients with infections was 168 patients/100 patient-years (95% CI: 100, 265) in patients treated with ENSPRYNG compared with 143 patients/100 patient-years (95% CI: 83, 229) in patients treated with placebo. The rate of patients with serious infections was 4 patients/100 patient-years (95% CI: 1, 15) in patients treated with ENSPRYNG compared with 10 patients/100 patient-years (95% CI: 2, 28) in patients receiving placebo.

Laboratory Abnormalities

Decreased Neutrophil Count

Of the patients treated with ENSPRYNG, 10% had neutrophils below 1×10^9/L compared to 9% in placebo in Study 1. In Study 2, 15% patients had neutrophils below 1×10^9/L compared to 4% in placebo. There was one patient in Study 1 treated with ENSPRYNG with neutrophil counts $< 0.5 \times 10^9$/L, and one patient in Study 2 discontinued ENSPRYNG because of neutropenia.

Decreased Platelet Count

In Study 1, a shift in platelet count decreases from normal at baseline to below the lower limit of normal (LLN) occurred in 26% of patients treated with ENSPRYNG compared to 5% of patients receiving placebo. In Study 2, decreases in platelet counts from normal at baseline to below the LLN occurred in 35% of patients treated with ENSPRYNG and in 17% of patients receiving placebo. None of the patients had a decrease in platelet count to less than 50×10^9/L.

Elevated Liver Enzymes

In Study 1, increases from normal at baseline to above ULN in ALT or AST occurred in 43% and 25% of patients treated with ENSPRYNG, respectively, compared to 13% and 9% of patients receiving placebo. In Study 2, increases from normal at baseline to above the ULN in ALT or AST occurred in 8% and 8% of patients treated with ENSPRYNG, respectively, compared to 12% and 19% of patients receiving placebo.

In Study 1 and Study 2 combined, elevations of ALT or AST greater than 3 times the ULN occurred in 3% of patients treated with ENSPRYNG, compared to no patients treated with placebo. These elevations were not associated with increases in total bilirubin. One patient receiving ENSPRYNG in Study 2 had an elevation of ALT above 5 times the ULN, which was observed 4 weeks after initiation of therapy, normalizing 78 days after discontinuation of ENSPRYNG.

Lipid Abnormalities

In Study 1 and Study 2, elevations in total cholesterol above 7.75 mmol/L (300 mg/dl) occurred in 12% and 15% of patients treated with ENSPRYNG, respectively, compared to no patients receiving placebo.

Elevations in triglycerides above 3.42 mmol/L (300 mg/dl) occurred in 27% and 12% of patients treated with ENSPRYNG in Study 1 and Study 2, respectively, compared to 13% and 8% of patients receiving placebo.

Fibrinogen Levels

In Study 1, the median percent reduction in fibrinogen was 38% in patients treated with ENSPRYNG compared to 5% in patients receiving placebo. In Study 2, the median percent reduction in fibrinogen level was 33% in patients treated with ENSPRYNG compared to 0% in patients receiving placebo.

Complement Levels

In Study 1, the median percent reduction in the C3 and C4 components of complement was 23% and 50% in patients treated with ENSPRYNG, respectively, compared to 0% and 1% patients receiving placebo. In Study 2, the median percent reduction in the C3 and C4 components of complement was 20% and 53% in patients treated with ENSPRYNG, respectively, compared to 0% and 1% in patients receiving placebo.

Body Weight

In the pool of Studies 1 and 2, body weight increases of at least 7% from baseline occurred in 28% of patients treated with ENSPRYNG compared to 8% of patients receiving placebo.

Body weight increases of at least 15% from baseline occurred in 4% of patients treated with ENSPRYNG compared to 4% of patients receiving placebo.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of anti-satralizumab-mwge antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In Study 1 and Study 2, anti-drug-antibodies (ADAs) were observed in 73% and 38% of patients receiving ENSPRYNG in the double-blind period, respectively. The ability of these ADAs to neutralize satralizumab-mwge binding is unknown. Patients with higher body weight and lower exposure were more likely to develop ADAs (irrespective of treatment with IST). Exposure was lower in ADA positive patients. Although anti-satralizumab-mwge antibody development was not found to affect the efficacy of ENSPRYNG in these patients, the available data are too limited to make definitive conclusions. Immunogenicity does not have a clinically-relevant impact on safety. Based on the available information, neither dose interruption nor modification is warranted in those patients who develop ADAs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENSPRYNG during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-277-9338.

Risk Summary

There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of satralizumab-mwge at doses up to 50 mg/kg/week *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Fetal/neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ENSPRYNG in utero *[see Warnings and Precautions (5.1)]*.

Data

Animal Data

Weekly subcutaneous administration of satralizumab-mwge (0, 2, or 50 mg/kg) to monkeys throughout pregnancy resulted in no adverse effects on postnatal development of the offspring; however, immune function was impaired in offspring at both doses. Plasma exposures (C_{ave}) in dams at the low and high doses were approximately 3 and 100 times, respectively, that in humans at the recommended monthly maintenance dose of 120 mg.

8.2 Lactation

Risk Summary

No information is available on the presence of satralizumab-mwge in human milk, the effects of the satralizumab-mwge on the breastfed infant, or the effects of the satralizumab-mwge on milk production. Satralizumab-mwge was excreted in the milk of lactating monkeys administered satralizumab-mwge throughout pregnancy. Human IgG is excreted in human milk and the potential for absorption in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and

any potential adverse effects on the breastfed infant from ENSPRYNG or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENSPRYNG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. However, population pharmacokinetic analyses in patients with NMOSD did not show that age affected the pharmacokinetics of satralizumab-mwge *[see Clinical Pharmacology (12.3)]*. In general, caution should be used when dosing the elderly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

11 DESCRIPTION

Satralizumab-mwge is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody based on a human IgG2 framework. Each light chain and heavy chain consists of 214 and 443 amino acids, respectively. Satralizumab-mwge is a glycoprotein with an approximate molecular weight of 143 kDa and is produced by recombinant DNA technology in Chinese hamster ovary cells. The binding of satralizumab-mwge to the IL-6 receptor is pH-sensitive.

ENSPRYNG (satralizumab-mwge) injection for subcutaneous administration is supplied as a sterile, clear, colorless to slightly yellow solution with no preservative with an approximate pH of 6. ENSPRYNG is supplied in a single-dose prefilled syringe. Each syringe delivers 1 mL of solution containing 120 mg of satralizumab-mwge, L-arginine (26.1 mg), L-histidine (3.1 mg), poloxamer 188 (0.5 mg), L-aspartic acid (pH adjustment), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which satralizumab-mwge exerts therapeutic effects in NMOSD is unknown but is presumed to involve inhibition of IL-6-mediated signaling through binding to soluble and membrane-bound IL-6 receptors.

12.2 Pharmacodynamics

The relationship between any of the pharmacodynamic effects of ENSPRYNG and clinical outcomes in NMOSD is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of ENSPRYNG have been characterized both in Japanese and Caucasian healthy volunteers, and in NMOSD patients. The pharmacokinetics in NMOSD patients using the recommended dose were characterized using population pharmacokinetic analysis methods based on a database of 154 patients.

The concentration-time course of ENSPRYNG in patients with NMOSD was accurately described by a two-compartment population pharmacokinetic model with parallel linear and target-mediated (Michaelis-Menten) elimination and first-order subcutaneous absorption. ENSPRYNG clearance and volume parameters allometrically scaled by body weight (through power function with the fixed power coefficient of 0.75 and 1 for clearance and volume parameters, respectively). Body weight was shown to be a significant covariate, with clearance and V_c for patients weighing 123 kg (97.5th percentile of the weight distribution) increased by 71.3% and 105%, respectively, compared to a patient weighing 60 kg.

Steady state pharmacokinetics were achieved after the loading period (8 weeks) as follows [mean (±SD)]: C_{min}: 19.7 (12.2) mcg/mL, C_{max}: 31.5 (14.9) mcg/mL, and AUC: 737 (386) mcg.mL/day.

Absorption

The bioavailability of satralizumab-mwge was 85%.

Distribution

Satralizumab-mwge undergoes biphasic distribution. The central volume of distribution was 3.46 L and the peripheral volume of distribution was 2.07 L. The inter-compartmental clearance was 0.336 L/day.

Elimination

The total clearance of satralizumab-mwge is concentration-dependent. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMOSD patients) is estimated to be 0.0601 L/day. The associated terminal $t_{1/2}$ is approximately 30 days (range 22 – 37 days) based on data pooled from Study 1 and Study 2.

Metabolism

The metabolism of satralizumab-mwge has not been directly studied, as antibodies are cleared principally by catabolism.

Excretion

Monoclonal antibodies, including satralizumab-mwge, are not eliminated via renal or hepatic pathways.

Specific Populations

Population pharmacokinetic analyses in patients with NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab-mwge.

Patients with Renal or Hepatic Impairment

No formal studies of the effect of renal impairment or hepatic impairment on the pharmacokinetics of satralizumab-mwge were conducted.

Drug Interaction Studies

No formal drug-drug interaction studies have been performed with ENSPRYNG.

Based on population pharmacokinetic analyses of the available data, the impact of commonly used small molecule drugs on the pharmacokinetics of satralizumab-mwge remains inconclusive.

Suppression of IL-6 signaling by treatment with ENSPRYNG, from the low baseline levels seen in Study 1 and Study 2, is expected to have a minor impact on exposure of concomitant medications metabolized by CYP450 enzymes. The clinical significance of this is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of satralizumab-mwge were not conducted.

Mutagenesis

Genetic toxicology studies of satralizumab-mwge were not conducted. As an antibody, satralizumab-mwge is not expected to interact directly with DNA.

Impairment of Fertility

In monkeys administered satralizumab-mwge (0, 2, 10, or 50 mg/kg) weekly by subcutaneous injection for 26 weeks, no effects on sperm, estrus cycle, or male and female reproductive organs

were observed. At the high dose, plasma exposures (C_{ave}) were approximately 100 times that in humans at the recommended monthly maintenance dose of 120 mg.

14 CLINICAL STUDIES

The efficacy of ENSPRYNG for the treatment of NMOSD in adult patients was established in two studies. Study 1 was a randomized (2:1), placebo-controlled trial in 95 patients without concurrent IST (Study 1, NCT02073279) in which 64 patients were anti-AQP4 antibody positive and 31 patients were anti-AQP4 antibody negative.

Study 2 was a randomized (1:1), placebo-controlled trial in 76 adult patients with concurrent IST (Study 2, NCT02028884). Of these, 52 adult patients were anti-AQP4 antibody positive and 24 adult patients were anti-AQP4 antibody negative.

Patients met the following eligibility criteria:

1. Study 1: Clinical evidence of 1 relapse in the previous 12 months
2. Study 2: Clinical evidence of at least 2 relapses in the previous 2 years, at least one of which must have occurred in the previous year
3. EDSS score of 0 to 6.5 (both studies)
4. Study 1: Patients were excluded if previously treated with IST within an interval specified for each such therapy
5. Study 2: One of the following baseline treatments at a stable dose as a monotherapy for 8 weeks prior to baseline: azathioprine, mycophenolate mofetil, oral corticosteroids

In Study 1, 41 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 23 received placebo. Females accounted for 76% of the ENSPRYNG group and 96% of the placebo group. The remaining baseline demographic characteristics were balanced between the treatment groups. The mean age was 44 years. Fifty percent were White, 22% were Black or African-American, and 20% were Asian. The mean EDSS score was 3.8.

In Study 2, 26 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 26 received placebo. All patients were receiving either concurrent azathioprine (42%), oral corticosteroids (52%), or mycophenolate mofetil (6%) during the trial. The baseline demographic and disease characteristics were balanced between the treatment groups. Females accounted for 100% of the study population. Forty-six percent of patients were White and 52% were Asian. The mean age was 46 years. The mean EDSS score was 4.0.

All potential relapses were adjudicated by a blinded Clinical Endpoint Committee (CEC). The primary efficacy endpoint for both studies was the time to the first CEC-confirmed relapse.

In Study 1, the time to the first CEC-confirmed relapse was significantly longer in ENSPRYNG-treated patients compared to patients who received placebo (risk reduction 55%; hazard ratio 0.45; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 74% risk reduction; hazard ratio 0.26; $p = 0.0014$ (Table 5; Figure 1). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

In Study 2, the time to the first CEC-confirmed relapse was significantly longer in patients treated with ENSPRYNG compared to patients who received placebo (risk reduction 62%; hazard ratio 0.38; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 78% risk reduction; hazard ratio 0.22; $p = 0.0143$ (Table 5; Figure 2). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

Table 5 Efficacy Results from Study 1 and Study 2 in anti-AQP4 Antibody Positive NMOSD Patients

	Study 1		Study 2	
	ENSPRYNG N=41	**Placebo N=23**	**ENSPRYNG + IST* N= 26**	**Placebo + IST N=26**
Time to Clinical Endpoint Committee (CEC)-Determined Relapse (Primary Efficacy Endpoint)				
Number (%) of Patients with Relapse	9 (22)	13 (56.5)	3 (11.5)	11 (42.3)
Hazard Ratio (95% CI)	0.26 (0.11, 0.63)		0.22 (0.06, 0.82)	
p-value	0.0014		0.0143	
Risk Reduction	74%		78%	
Proportion of Protocol Defined Relapse-Free Patients at 96 Weeks	76.5%	41.1%	91.1%	56.8%

* IST = immunosuppressant therapy

Figure 1 Study 1: Time to First CEC-Determined NMOSD Relapse in the Randomized Controlled Period in the ITT Population Anti-AQP4 Antibody Positive Patients

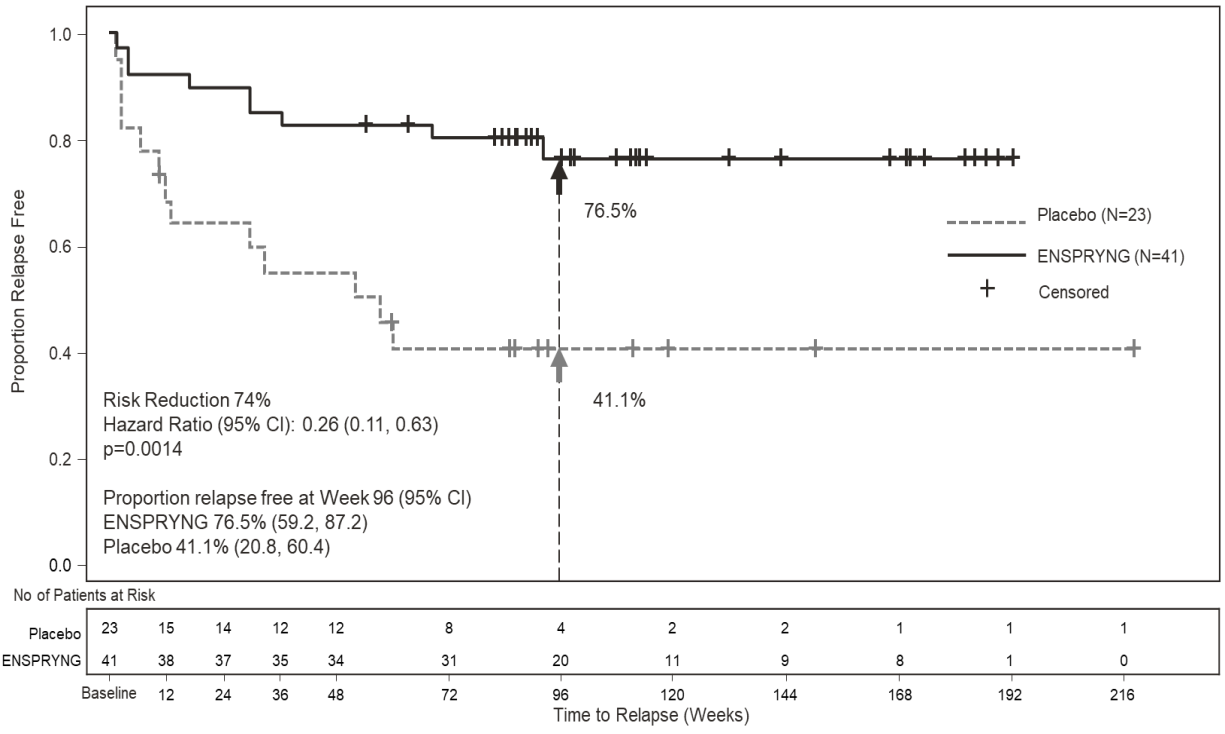
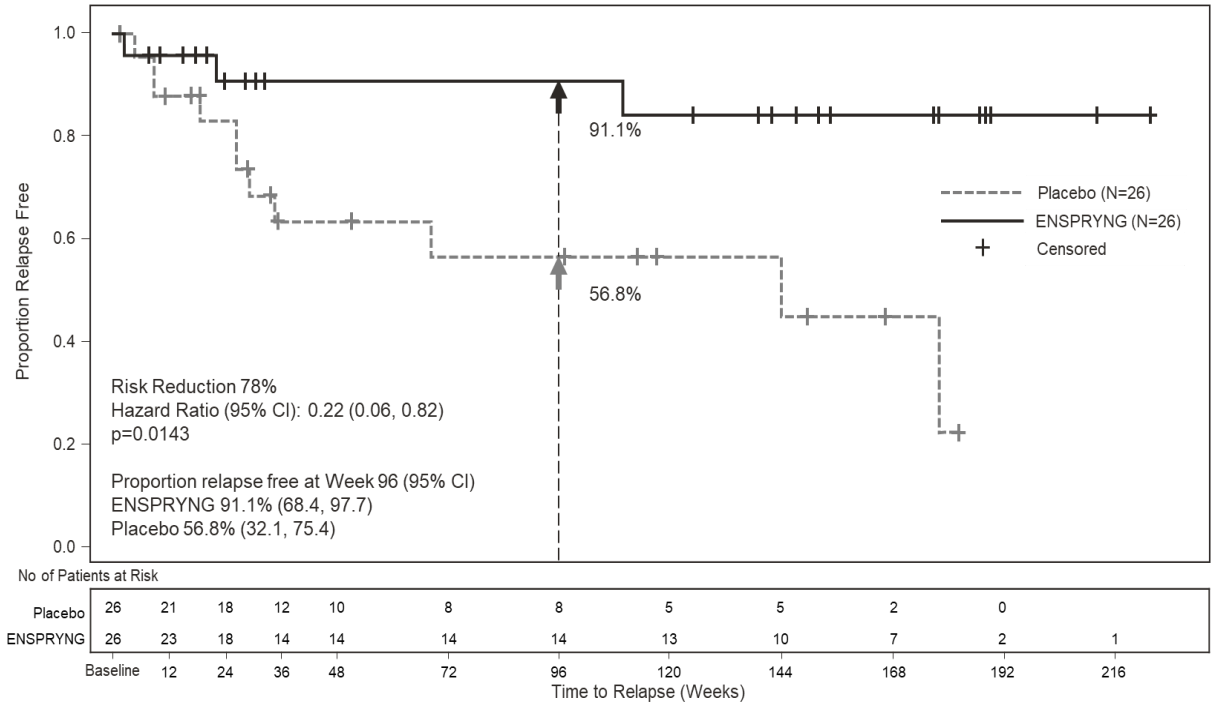


Figure 2 Study 2: Time to First CEC-Determined NMOSD Relapse in the Randomized Controlled Period in the ITT Population Anti-AQP4 Antibody Positive Patients



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ENSPRYNG (satralizumab-mwge) injection is available as a sterile, preservative-free, clear, colorless to slightly yellow solution in single-dose prefilled syringe (PFS) with needle safety device.

ENSPRYNG PFS is not made with natural rubber latex. Each ENSPRYNG carton contains one single-dose 120 mg/mL prefilled syringe (NDC 50242-007-01).

16.2 Storage and Handling

- Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
- Prior to administration, ENSPRYNG, if unopened, can be removed from and returned to the refrigerator, if necessary. The total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that an increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG. Instruct patients to contact their healthcare provider immediately when symptoms suggesting infection (e.g., fever, chills, constant cough, or sore throat) appear during treatment *[see Warning and Precautions (5.1)]*.

Vaccinations

Advise patients to complete any required vaccinations at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines *[see Warnings and Precautions 5.1]*.

Elevated Liver Enzymes

Inform patients on the importance of liver enzyme testing *[see Warnings and Precautions (5.2)]*.

Decreased Neutrophil Counts

Inform patients on the importance of neutrophil count testing *[see Warnings and Precautions (5.3)]*.

Hypersensitivity Reactions

Inform patients about the signs and symptoms of hypersensitivity reactions and anaphylaxis and advise them to contact their healthcare provider immediately if these symptoms occur *[see Warnings and Precautions (5.4)]*.

Instruction on Injection Technique

Instruct patients and caregivers to read the Instructions for Use before the patient starts using ENSPRYNG, and each time the patient gets a refill as there may be new information they need to know.

Perform the first injection under the guidance of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ENSPRYNG, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ENSPRYNG and the suitability for home use *[see Dosage and Administration (2.3) and Instructions for Use]*.

Instruct patients to remove the prefilled syringe from the refrigerator prior to use and allow to sit at room temperature outside of the carton for 30 minutes. Do not warm ENSPRYNG in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of syringes should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper prefilled syringe disposal, and caution against reuse of these items.

Pregnancy Exposure Registry

Encourage patients to enroll in the ENSPRYNG Pregnancy Registry if they become pregnant while taking ENSPRYNG. The Registry monitors fetal outcomes of pregnant women exposed to ENSPRYNG *[see Use in Specific Populations (8.1)]*.

ENSPRYNG® [satralizumab-mwge]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

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MEDICATION GUIDE

ENSPRYNG® (en-spryng)
(satralizumab-mwge)
injection, for subcutaneous use

What is the most important information I should know about ENSPRYNG?

ENSPRYNG may cause serious side effects including:

1. **Infections.** ENSPRYNG can increase your risk of serious infections some of which can be life-threatening. Talk to your healthcare provider if you are being treated for an infection or call them right away if you think you have signs of an infection, with or without a fever, such as:
    - chills, feeling tired, muscle aches, cough that will not go away or a sore throat
    - skin redness, swelling, tenderness, pain or sores on your body
    - diarrhea, belly pain, or feeling sick
    - burning when you urinate or urinating more often than usual

    Your healthcare provider will check if you have an infection and treat it if needed before you start or continue to take ENSPRYNG.
- Your healthcare provider should test you for hepatitis and tuberculosis (TB) before you start taking ENSPRYNG.
- All required vaccinations should be completed before starting ENSPRYNG. People using ENSPRYNG should not be given 'live' or 'live-attenuated' vaccines. 'Live' or 'live-attenuated' vaccines should be given at least 4 weeks before you start ENSPRYNG. Your healthcare provider may recommend that you get a 'non-live' (inactivated) vaccine, such as some of the seasonal flu vaccines. If you plan to get a 'non-live' (inactivated) vaccine, it should be given, whenever possible, at least 2 weeks before you start ENSPRYNG.

2. **Increased liver enzymes.**

    Your healthcare provider should order blood tests to check your liver enzymes before and while you are taking ENSPRYNG. Your healthcare provider will tell you how often you will need to have these blood tests. Make sure you get all of your follow-up blood tests as ordered by your healthcare provider. Your healthcare provider will tell you if you need to wait to start ENSPRYNG if your liver enzymes are increased.
3. **Low neutrophil count.**

    ENSPRYNG can cause a decrease in your neutrophil counts in your blood. Neutrophils are white blood cells that help the body fight off bacterial infections. Your healthcare provider should order blood tests to check your neutrophil count while you are taking ENSPRYNG.

See "What are the possible side effects with ENSPRYNG?"

What is ENSPRYNG?

ENSPRYNG is a prescription medicine used to treat neuromyelitis optica spectrum disorder (NMOSD) in adults who are aquaporin-4 (AQP4) antibody positive.

It is not known if ENSPRYNG is safe and effective in children.

Do not take ENSPRYNG if you:

- are allergic to satralizumab-mwge or any of the ingredients in ENSPRYNG. See **"What are the ingredients in ENSPRYNG?"** at the end of this Medication Guide for a complete list of ingredients in ENSPRYNG.
- have an active hepatitis B infection.
- have active or untreated inactive (latent) TB.

Before you take ENSPRYNG, tell your healthcare provider about all of your medical conditions, including if you:

- have or think you have an infection. See **"What is the most important information I should know about ENSPRYNG?"**
- have liver problems.
- have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have had or have been in contact with someone with tuberculosis.
- have had a recent vaccination or are scheduled to receive any vaccination.
- are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if ENSPRYNG will harm your unborn baby.
    - **Pregnancy Registry**: There is a registry for pregnant women who take ENSPRYNG. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking ENSPRYNG, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-833-277-9338 to enroll.
- are breastfeeding or plan to breastfeed. It is not known if ENSPRYNG passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ENSPRYNG.

Tell your healthcare provider about all the medicines you are taking, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take ENSPRYNG?

- ENSPRYNG is provided as a solution in a single-dose, prefilled syringe of 120 mg/mL of satralizumab-mwge.
- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject ENSPRYNG.
- ENSPRYNG is given by an injection under the skin (subcutaneously). If your healthcare provider decides that you or your caregiver can give your injections of ENSPRYNG, you or your caregiver should receive training on the right way to prepare and inject ENSPRYNG.
- Always inject all of the medicine in the syringe.
- The first 3 injections (loading period) of ENSPRYNG are taken 1 time every 2 weeks.
- After this, injection of ENSPRYNG is taken every 4 weeks (maintenance period). Keep taking ENSPRYNG 1 time every 4 weeks for as long as your healthcare provider tells you to.
- If you miss a dose of ENSPRYNG, talk to your health care provider about restarting dosing.

What are the possible side effects of ENSPRYNG?

ENSPRYNG may cause serious side effects, including:

- See **"What is the most important information I should know about ENSPRYNG?"**
- **Serious allergic reactions.** Serious allergic reactions that may be life-threatening have happened with other medicines like ENSPRYNG. Tell your healthcare provider before taking your next dose if you had hives, rash, or flushing after your injection. Seek medical attention right away if you have any symptoms of a serious allergic reaction, such as:
  - shortness of breath or trouble breathing
  - dizziness or feeling faint
  - swelling of your lips, face, or tongue
  - moderate or severe stomach (abdominal) pain or vomiting
  - chest pain
- The most common side effects of ENSPRYNG include:
  - sore throat, runny nose (nasopharyngitis)
  - rash
  - fatigue
  - extremity pain
  - headache
  - upper respiratory tract infection
  - nausea
  - inflammation of the stomach lining (gastritis)
  - joint pain

These are not all the possible side effects of ENSPRYNG.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

How should I store ENSPRYNG?

- Store ENSPRYNG in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton.
- Protect from light.
- **Do not** freeze or use the syringe if it has been frozen.
- **Do not** shake.
- ENSPRYNG, if unopened, can be removed from and returned to the refrigerator, if needed. The total combined time out of the refrigerator should not be more than 8 days at a temperature that does not go above 86°F (30°C).

General information about the safe and effective use of ENSPRYNG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENSPRYNG for a condition for which it was not prescribed. Do not give ENSPRYNG to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ENSPRYNG that is written for health professionals.

What are the ingredients in ENSPRYNG?

Active ingredient: satralizumab-mwge

Inactive ingredients: L-arginine, L-histidine, poloxamer 188, L-aspartic acid, and Water for Injection.

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
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For more information, go to www.ENSPRYNG.com or call 1-844-NSPRYNG.
This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 3/2022