Long-term efficacy of satralizumab in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) from SAkuraSky and SAkuraStar

Supplementary materials

Authors

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Detailed inclusion and exclusion criteria for the SAkura studies

SAkuraSky: inclusion criteria

1. Patients diagnosed as having either:
    - NMO as defined by Wingerchuk et al. 2006[1], which required the following:
        i. Optic neuritis
        ii. Acute myelitis
        iii. At least two of three supportive criteria:
            1. Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
            2. Brain MRI not meeting diagnostic criteria for MS
            3. NMO-immunoglobulin G (IgG) (anti-AQP4 antibody) seropositive status
    - NMOSD as defined by either of the following criteria with anti-AQP4 antibodies seropositive status at screening (Wingerchuk 2007[2]):
        i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion)
        ii. Optic neuritis: recurrent or simultaneous bilateral
2. Clinical evidence of at least 2 documented relapses (including first attack) in the last 2 years prior to screening, at least one of which had occurred in the 12 months prior to screening.
3. Expanded Disability Status Scale (EDSS) score from 0 to 6.5 inclusive at screening.
4. Age 12 to 74 years, inclusive at the time of informed consent.

5. One of the following baseline treatments at stable dose as a monotherapy for 8 weeks prior to baseline:
    i. Azathioprine
    ii. Mycophenolate mofetil
    iii. Oral corticosteroids
    - Adolescents had the option of oral corticosteroids in addition to azathioprine or mycophenolate mofetil
6. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

SAkuraSky: exclusion criteria

Prior therapies

1. Any previous treatment with interleukin-6 (IL-6) inhibitory therapy (e.g. tocilizumab), alemtuzumab, total body irradiation or bone marrow transplantation at any time.
2. Any previous treatment with anti-CD20, eculizumab, belimumab, interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide or dimethyl fumarate within 6 months prior to baseline.
3. Any previous treatment with anti-CD4, cladribine or mitoxantrone within 2 years prior to baseline
4. Treatment with any investigational agent within 3 months prior to baseline.

General safety

5. Pregnancy or lactation.
6. For patients of reproductive potential, a positive result from a serum pregnancy test at screening, or not willing to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug.
7. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
8. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
9. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.

10. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
11. Evidence of chronic active hepatitis B or C.
12. History of drug or alcohol abuse within 1 year prior to baseline.
13. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
14. Evidence of active TB (excluding patients receiving chemoprophylaxis for latent TB infection).
15. Evidence of active interstitial lung disease.
16. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
17. History of malignancy within the last 5 years, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured).
18. History of severe allergic reaction to a biologic agent (e.g. shock, anaphylactic reactions).
19. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.

Laboratory exclusion criteria (at screening)

20. Following laboratory abnormalities at screening*:
    i. White blood cells (WBC) <3.0 ≥10^3/μL
    ii. Absolute neutrophil count (ANC) <2.0 ≥10^3/μL
    iii. Absolute lymphocyte count <0.5 ≥10^3/μL
    iv. Platelet count <10 ≥10^4/μL
    v. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 times the upper limit of normal (ULN).

SAkuraStar: inclusion criteria

1. Patients diagnosed as having either:
    - NMO as defined by Wingerchuk et al. 2006[1], which required the following:
        i. Optic neuritis
        ii. Acute myelitis
        iii. At least two of three supportive criteria:
            1. Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
            2. Brain MRI not meeting diagnostic criteria for MS

3. NMO-immunoglobulin G (IgG) (anti-AQP4 antibody) seropositive status
   - NMOSD as defined by either of the following criteria with anti-AQP4 antibodies seropositive status at screening (Wingerchuk 2007[2]):
     i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion)
     ii. Optic neuritis: single, recurrent or simultaneous bilateral
2. Clinical evidence of at least 1 documented relapse (including first attack) in the last 12 months prior to screening
3. Expanded Disability Status Scale (EDSS) score from 0 to 6.5 inclusive at screening.
4. Age 18 to 74 years, inclusive at the time of informed consent.
5. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

SAkuraStar: exclusion criteria

Exclusion criteria related to NMOSD

1. Clinical relapse onset (including first attack) within 30 days prior to baseline.

Prior therapies

2. Any previous treatment with IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation or bone marrow transplantation at any time.
3. Any previous treatment with anti-CD20, eculizumab, anti-B-lymphocyte stimulator (BLyS) monoclonal antibody (e.g., belimumab), any other treatment for prevention of MS relapse (e.g., interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide or dimethyl fumarate) within 6 months prior to baseline.
4. Any previous treatment with anti-CD4, cladribine, cyclosphosphamide or mitoxantrone within 2 years prior to baseline.
5. Treatment with any investigational agent within 3 months prior to baseline.

General safety – see SAkuraSky criteria, plus:

See SAkuraSky criteria, plus:

6. History of Stevens-Johnson syndrome.

Laboratory exclusion criteria (at screening)

See SAkuraSky criteria.

Protocol-defined relapse criteria

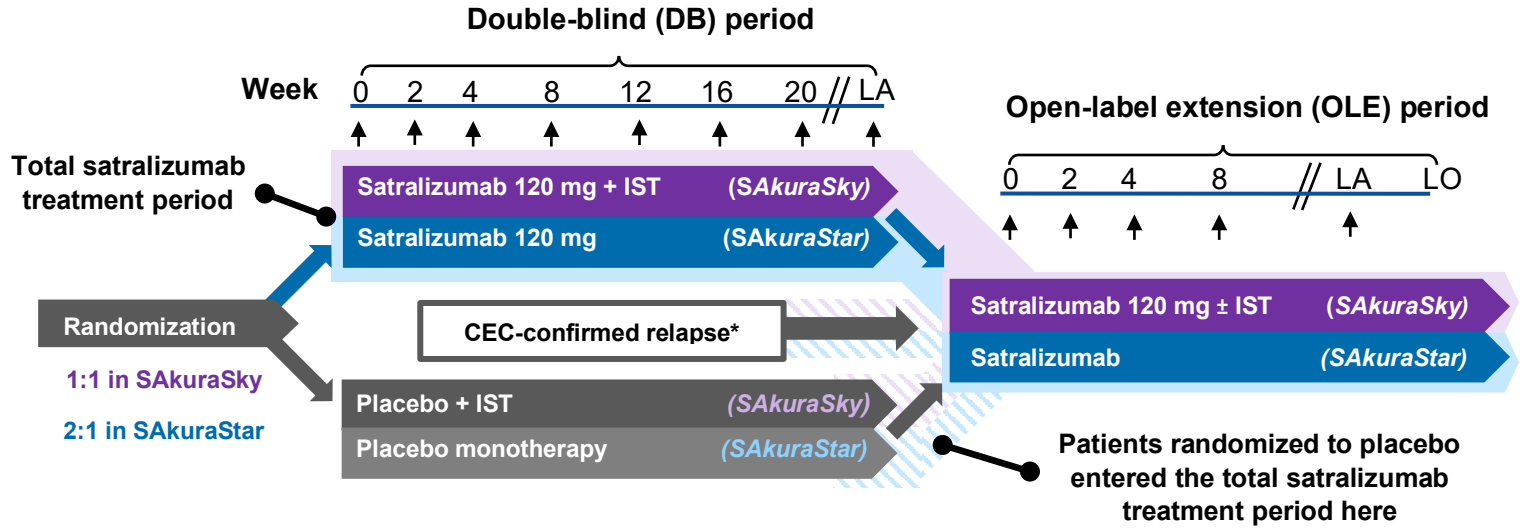
The primary endpoint of both studies was time to first protocol-defined relapse (PDR). PDRs were new or worsening objective neurological symptoms with at least one of the following:

- Increase of ≥1.0 EDSS points from a baseline EDSS score of >0 (or ≥2.0 EDSS points from a baseline EDSS score of 0)
- Increase of ≥2.0 points on ≥1 appropriate symptom-specific functional system scores (FSS) for either pyramidal, cerebellar, brainstem, sensory, bowel or bladder, or a single eye
- Increase of ≥1.0 points on ≥2 symptom-specific FSS with a baseline of ≥1.0
- Increase of ≥1.0 points on a single-eye symptom-specific FSS with a baseline score of ≥1.0

Symptoms must be attributable to NMOSD, persisting for more than 24 hours, and not attributable to confounding clinical factors such as fever, infection, injury, change in mood, or adverse reactions to medications. EDSS and FSS were assessed within 7 days of a patient reporting their symptoms. PDRs were adjudicated by an independent Clinical Endpoint Committee (CEC).

Supplementary tables and figures

eFigure 1: SAkuraSky and SAkuraStar study designs

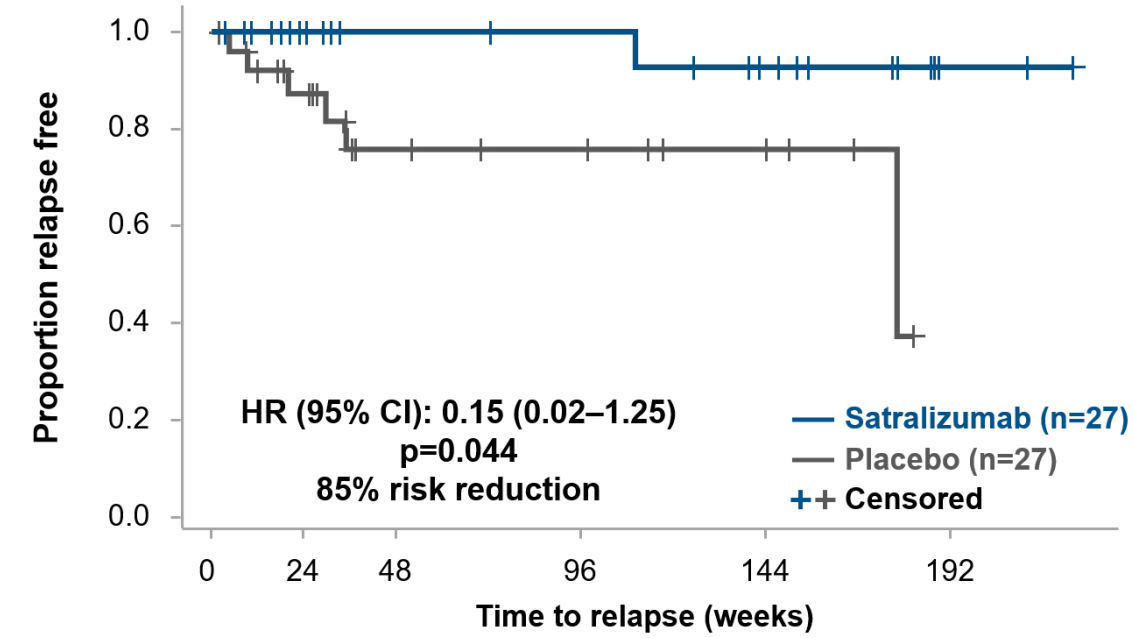


CEC, Clinical Endpoint Committee; IST, immunosuppressive therapy; OST, overall satralizumab treatment period; LA, last administration; LO, last observation

↑ Treatment administered. *CEC-confirmed protocol-defined relapse or clinical relapse requiring rescue therapy in SAkuraSky; CEC-confirmed protocol-defined relapse in SAkuraStar.

eFigure 2: Kaplan-Meier analysis of time to first severe PDR in the double-blind periods of a) SAkuraSky and b) SAkuraStar

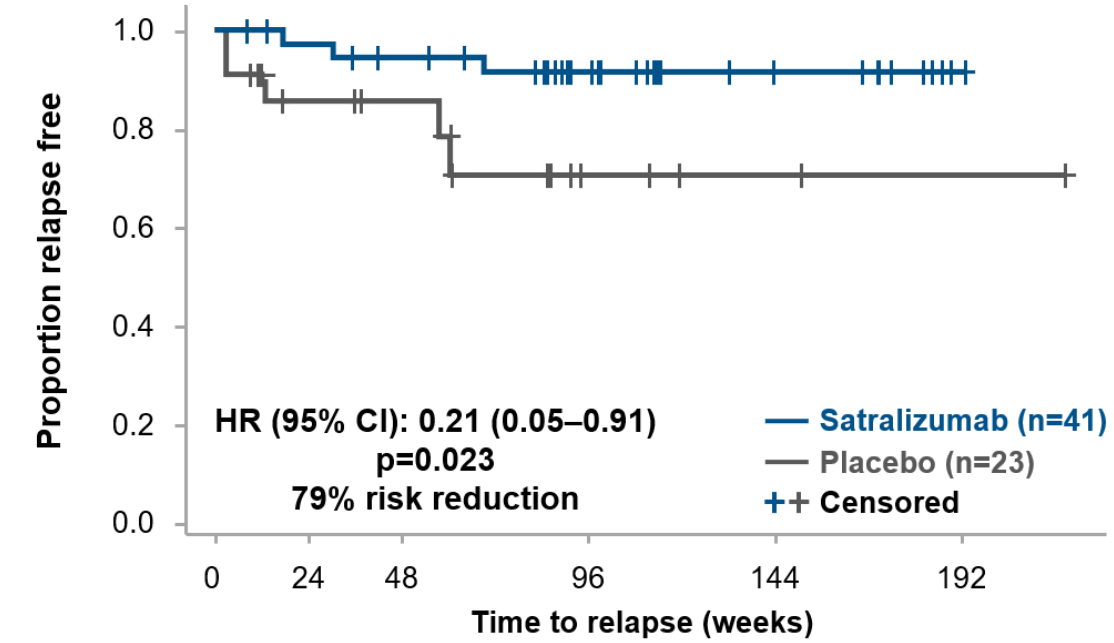
a)



Number at risk

Placebo	27	22	19	13	10	8	8	5	5	2	0	
Satralizumab	27	24	19	15	15	15	14	13	10	7	2	1

b)



Number at risk

Placebo	23	17	14	14	12	8	4	2	2	1	1	1
Satralizumab	41	40	37	35	34	31	21	11	9	8	1	0

References

1. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. May 23 2006;66(10):1485-9. doi:10.1212/01.wnl.0000216139.44259.74

2. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *The Lancet Neurology*. 2007;6(9):805-815. doi:10.1016/S1474-4422(07)70216-8