OCEANIC-STROKE: Asundexian for Secondary Stroke Prevention

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Oral faCtor Eleven A iNhibitor asundexIan as novel antithromboti C (OCEANIC) – STROKE was a phase 3 double-blind placebo-controlled clinical trial that explored whether the addition of asundexian to an antiplatelet medication regimen in patients with noncardioembolic stroke would further reduce secondary stroke risk. The physiologic rationale for the study was based on findings in patients with genetic factor XI deficiency which has been associated with a reduced risk of ischemic stroke while also not increasing the risk of intracerebral hemorrhage; additionally, patients with increased factor XI levels have been found to have a higher risk of ischemic stroke. Asundexian is a drug that inhibits activated factor XI by more than 90%, and its addition to either a dual or single antiplatelet regimen could further reduce the risk of secondary ischemic stroke.

The study was conducted at 702 centers in 37 countries. Patients targeted for enrollment were those ≥18 years of age, with noncardioembolic stroke with a maximum National Institutes of Health Stroke Scale (NIHSS) score of 15, or high-risk transient ischemic attack (TIA) with an $ABCD^2$ score of 6 or 7, that could be randomized to either asundexian 50 mg once daily or placebo given along with a prescribed dual or single antiplatelet agent, with administration of the first dose of asundexian or placebo within 72 hours from stroke onset (and within 4 hours from time of enrollment). Patients also had to have at least one of the following findings: 1) imaging documented non-lacunar infarct; 2) an atherosclerosis history that could include carotid atheroma with 50% stenosis, peripheral vascular or coronary artery disease; and/or 3) an atherosclerotic plaque on neurovascular imaging in the aortic arch, or the intra- or extra-cranial vasculature (did not have to be located within vascular anatomic territory of the stroke or TIA event). Treatment with intravenous thrombolysis or endovascular thrombectomy was allowable, with these patients enrolled after 24 hours had passed. Exclusions included conditions warranting treatment with anticoagulation, bleeding conditions or findings deemed to be clinically important, and stroke occurring due to a procedure (e.g. coronary bypass, etc.) or other specific/unusual cause (e.g. vasculitis, sickle cell, etc.). If atrial fibrillation was ultimately documented, asundexian or placebo and antiplatelet medication were discontinued, and anticoagulation was prescribed.

The primary efficacy endpoint was occurrence of an ischemic stroke, while a secondary outcome was a composite of acute

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myocardial infarction, TIA or stroke, and all-cause death. The safety endpoint was major bleeding, defined by the International Society on Thrombosis and Haemostasis (ISTH) as bleeding causing death, symptomatic bleeding in a critical area or organ, and overt bleeding resulting in decreased hemoglobin requiring treatment (≥2 g per deciliter or requiring transfusion of ≥2 units of packed red blood cells or whole blood). Secondary safety outcomes included relevant nonmajor bleeding, any symptomatic intracranial hemorrhage or hemorrhagic stroke, and both fatal and minor bleeding. Patient follow-up was performed at 1 and 3 months, after which patients were followed at 3-month intervals. An intention to treat approach was utilized for analyses.

Enrollment occurred from January 2023 through February 2025, resulting in a total of 12,327 patients randomized (6162 asundexian and 6165 placebo); of these patients, 73 never received asundexian, 45 patients withdrew study consent, and 39 patients were lost to follow-up. Baseline characteristics were similar between the asundexian and placebo groups. Patients were on average 68 years of age, a third were women, two-thirds were White race, median baseline NIHSS was 2 points, and most (94.7%) were diagnosed with ischemic stroke with the remaining patients high-risk TIA cases. Overall, 27.4% of ischemic stroke patients received intravenous thrombolysis and/or endovascular thrombectomy prior to enrollment and randomization, and 62.6% had dual antiplatelet therapy planned for initiation. The most common ischemic stroke mechanism was large artery atheroma (42.8%), with 29.9% of patients having stroke of undetermined cause, and 22.6% having a small vessel etiology. Median time for trial follow-up was 567 days (or 1.55 years) from the time of randomization.

The ischemic stroke primary outcome occurred in 6.2% of asundexian treated patients and 8.4% of placebo group patients (HR 0.74; 95% CI 0.65 to 0.84; $p<0.001$).

New stroke (ischemic or hemorrhagic) occurred in 6.6% of asundexian patients compared to 8.8% of placebo group patients (HR 0.74; 95% CI, 0.65 to 0.84; $p<0.001$) and cardiovascular deaths occurred in 9.2% of asundexian patients compared to 11.1% of placebo group patients (HR 0.83; 95% CI, 0.74 to 0.92; $p<0.001$); combined all-cause deaths, myocardial infarction, and stroke occurred in 10.5% of asundexian patients and 12.3% of placebo group patients (HR 0.85; 95% CI, 0.77 to 0.95; $p=0.003$).

The occurrence of ISTH-defined major bleeding was similar between groups, occurring in 1.9% of asundexian patients compared to 1.7% of placebo group patients (HR 1.10; 95% CI, 0.85 to 1.44; $p=0.46$). Incidence of major or clinically relevant nonmajor bleeding was also similar between groups at 5.5% asundexian patients and 5.0% placebo patients (HR 1.12; 95% CI, 0.96 to 1.30; $p=0.16$), and the incidence of other secondary safety outcomes (symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, and minor bleeding) was also similar between the asundexian and placebo groups.

The authors concluded that the addition of asundexian to an antiplatelet treatment regimen, initiated within 72 hours from

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stroke onset in patients with ischemic stroke or high-risk TIA is associated with a lower risk of secondary ischemic stroke without an increase in major bleeding. The authors noted that the study's findings were consistent with both epidemiologic and mendelian randomization studies that have documented lower risk of ischemic stroke among those with lower factor XI levels.

At the time of this writing, it remains unknown exactly what antiplatelet regimens were prescribed in the study since this information was not included in the *New England Journal of Medicine* publication or its supplemental files; however, most patients received dual antiplatelet agents alongside asundexian. We also do not yet know how long dual antiplatelets were prescribed (e.g. 21-days?). Despite this, the study provides compelling evidence that approximates a short dual antiplatelet regimen, with the cumulative incidence Aalen–Johansen curve diverging to favor asundexian early into antiplatelet treatment and likely close to the time of discontinuation of a second antiplatelet agent. This is also consistent with the median NIHSS of 2 points for the sample suggesting minor stroke with a short dual antiplatelet duration.

Study limitations include the broad inclusion criteria for stroke severity and the enrollment of few patients with NIHSS scores ≥8 points, the small number of high-risk TIA patients enrolled, and the lack of racial diversity in the sample with most patients enrolled in Australia, western Europe, and Israel.

At the time of this writing, asundexian is not approved by the United States Food and Drug Administration or other regulatory agencies around the world, so it is not yet commercially available. Stroke clinicians should look forward to the agent's release worldwide as what could be an essential addition to drug formularies that is capable of reducing secondary ischemic stroke risk with no increased risk of major bleeding.

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