

Original Article

Asundexian for Secondary Stroke Prevention: Factor Xla Inhibition and the OCEANIC-STROKE Trial

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Abstract: Patients surviving a non-cardioembolic ischemic stroke or high-risk transient ischemic attack (TIA) face a substantially elevated risk of recurrent stroke despite current antiplatelet-based secondary prevention. Asundexian is an investigational oral small-molecule inhibitor of activated factor Xla (FXla) that targets the contact activation pathway of coagulation, offering potential thrombus prevention without impairment of primary hemostasis. The OCEANIC-STROKE trial was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled, event-driven study. A total of 12,327 patients were enrolled within 72 hours of a qualifying event across 37 countries and randomized to asundexian 50 mg once daily or placebo, on top of planned single or dual antiplatelet therapy. The primary efficacy endpoint was time to ischemic stroke; the primary safety endpoint was ISTH-defined major bleeding. Asundexian significantly reduced the incidence of ischemic stroke compared with placebo (6.2% vs. 8.4%; cause-specific hazard ratio [csHR], 0.74; 95% CI, 0.65–0.84; $P < 0.001$), representing a 26% relative risk reduction. Major bleeding was similar in both groups (1.9% vs. 1.7%; csHR, 1.10; 95% CI, 0.85–1.44). Consistent benefit was demonstrated across all prespecified subgroups, including stroke subtype, index event, use of reperfusion therapy, age, sex, and antiplatelet strategy. OCEANIC-STROKE is the first successful phase 3 trial of a factor Xla inhibitor for secondary stroke prevention, demonstrating that asundexian reduces recurrent ischemic stroke without increasing major bleeding, potentially establishing a new therapeutic paradigm for this high-risk population.

Keywords: asundexian, factor Xla inhibitor, secondary stroke prevention, non-cardioembolic ischemic stroke

1. INTRODUCTION

Ischemic stroke is one of the most devastating neurological conditions globally, affecting approximately 12 million people annually and representing a leading cause of death and long-term disability. Among those who survive an initial ischemic event, the risk of a recurrent stroke is substantial, estimated at 20–30% within five years, with the highest concentrations of risk occurring in the first 90 days following the index event [1,2]. This persistent vulnerability underscores a critical unmet clinical need: the development of safer and more effective pharmacological strategies for secondary stroke prevention. Current guideline-recommended secondary prevention following non cardioembolic ischemic stroke or high-risk TIA relies primarily on antiplatelet therapy—specifically aspirin, clopidogrel, or combinations thereof. While these

agents reduce the risk of recurrent vascular events, their absolute risk reduction is modest, and prolonged dual antiplatelet therapy (DAPT) carries a clinically meaningful risk of major bleeding complications, limiting long-term utility [3]. Direct oral anticoagulants (DOACs), which have revolutionized stroke prevention in atrial fibrillation, have not demonstrated net clinical benefit in non-cardioembolic stroke settings, largely due to unacceptable hemorrhagic risk. Against this backdrop, the biology of factor XI (FXI) has emerged as a compelling therapeutic target. Epidemiological and genetic data consistently demonstrate that individuals with naturally low FXI levels or hereditary FXI deficiency experience significantly reduced rates of ischemic stroke and venous thromboembolism, without a commensurate increase in intracranial hemorrhage or spontaneous bleeding [4]. This dissociation between thrombosis and hemostasis reflects FXI's differential role in pathological thrombus amplification versus physiological clot formation—a distinction that offers a unique opportunity to "uncouple" antithrombotic efficacy from bleeding liability. Asundexian (BAY 2433334) is a novel, orally bioavailable, once-daily small-molecule inhibitor of activated factor XIa (FXIa) developed by Bayer AG. By selectively targeting FXIa, asundexian aims to reduce pathological thrombus propagation while preserving primary hemostatic responses. Following encouraging phase 2 data from the PACIFIC-Stroke trial and pharmacological characterization, asundexian advanced to the landmark phase 3 OCEANIC-STROKE trial—the first phase 3 study of a FXIa inhibitor to complete evaluation for secondary stroke prevention. This review provides a comprehensive synthesis of the scientific rationale, clinical development pathway, trial design, principal results, subgroup analyses, safety profile, and clinical implications of asundexian, with particular focus on the OCEANIC-STROKE trial published in the *New England Journal of Medicine* in April 2026.

2. PATHOPHYSIOLOGY AND THERAPEUTIC RATIONALE

The coagulation cascade is classically divided into extrinsic (tissue factor-mediated) and intrinsic (contact activation) pathways, converging on a common pathway through factor X activation, ultimately generating thrombin and fibrin. Factor XI occupies a pivotal position within the intrinsic pathway, being activated both by factor XIIa in the classical contact activation sequence and by thrombin in a positive feedback loop that amplifies and sustains clot formation [5]. Critically, FXIa plays a more prominent role in propagating pathological arterial and venous thrombi—particularly those forming on disrupted endothelium or activated surfaces—than in the initial hemostatic plug formation that arrests bleeding at sites of vascular injury. The latter process depends more heavily on tissue factor and platelet activation than on the amplification loop involving FXI. This mechanistic divergence has been validated in preclinical models: FXI knockout or FXIa inhibition in murine and primate models substantially reduces thrombotic events with minimal prolongation of bleeding time [6]. Population-based epidemiological studies provide compelling evidence that FXI activity levels are directly correlated with ischemic stroke risk. Individuals with congenital factor XI deficiency (hemophilia C) have markedly reduced rates of ischemic stroke and deep vein thrombosis, while experiencing relatively preserved surgical hemostasis and a distinct absence of the spontaneous joint and muscle bleeding characteristic of hemophilia A and B [7]. Analyses from the Leiden Thrombophilia Study and other large cohorts confirm that mild or moderate FXI deficiency is associated with 43–48% reductions in arterial thrombotic events including MI, stroke, and TIA compared with general population controls [8]. These observations suggest that FXI inhibition could provide meaningful antithrombotic protection against ischemic stroke without the excess hemorrhagic risk that has historically limited the use of anticoagulant agents in non-cardioembolic stroke populations. The development of small-molecule FXIa inhibitors like asundexian was directly motivated by this human genetic validation.

3. PHARMACOLOGICAL PROFILE OF ASUNDEXIAN

Asundexian (BAY 2433334) is a direct, reversible, small-molecule inhibitor of activated factor XIa. It binds selectively to the active site of FXIa, preventing substrate cleavage and downstream activation of factor IX. Key pharmacological properties include: oral bioavailability suitable for once-daily administration; rapid onset of FXIa inhibition; dose-dependent suppression of FXIa activity; renal elimination with a half-life supporting predictable pharmacokinetics; and minimal clinically relevant interactions with the cytochrome P450 system [9]. In vitro and ex vivo studies demonstrate that asundexian prolongs the activated partial thromboplastin time (aPTT) in a dose-dependent manner, reflecting its intrinsic pathway activity, without affecting prothrombin time (PT), indicating specificity for the contact activation rather than the extrinsic pathway. At the 50 mg dose selected for phase 3 trials, near-complete FXIa suppression (>90% inhibition) is achieved at steady-state plasma concentrations, providing robust antithrombotic coverage throughout the dosing interval [9]. Early-phase studies of asundexian established its pharmacokinetic and pharmacodynamic profile across a range of doses in healthy volunteers and in patients with specific conditions including atrial fibrillation and end-stage renal disease. The PACIFIC-AF phase 2 study (n=753) compared asundexian 20 mg and 50 mg once daily to apixaban in patients with non-valvular atrial fibrillation, demonstrating markedly lower rates of clinically relevant bleeding with asundexian, though this study was not powered to assess thrombotic efficacy [10]. These data provided reassurance regarding the favorable bleeding profile and supported the selection of 50 mg once daily as the dose for phase 3 evaluation.

4. THE PACIFIC-STROKE PHASE 2B TRIAL

The PACIFIC-Stroke trial was a pivotal phase 2b, international, randomized, double-blind, placebo-controlled, dose-finding study that enrolled 1,808 patients with acute non cardioembolic ischemic stroke within 48 hours of symptom onset. Patients were randomized to asundexian 10 mg, 20 mg, or 50 mg once daily, or placebo, all administered on top of dual antiplatelet therapy (aspirin plus clopidogrel), for 26 weeks [11]. The primary efficacy endpoint was a composite of covert brain infarction on MRI and recurrent symptomatic ischemic stroke at 26 weeks. While the primary composite endpoint was not significantly different between asundexian and placebo groups—in part attributable to the high rates of asymptomatic covert infarction that may not respond to antithrombotic therapy—a pre-specified exploratory analysis focusing on symptomatic ischemic stroke showed a numerically consistent reduction with asundexian across all doses. Importantly, there was no statistically significant increase in ISTH major bleeding across asundexian doses compared to placebo, a critical safety finding that distinguished the agent from conventional anticoagulants [11]. The 50 mg once-daily dose was selected for phase 3 development based on its pharmacodynamic profile achieving near-complete FXIa inhibition and the numerical trends toward efficacy in symptomatic stroke reduction. PACIFIC-Stroke was the first completed randomized trial of a factor XIa inhibitor in non-cardioembolic stroke, providing the foundational rationale for OCEANIC-STROKE. Concurrently with the stroke program, asundexian was evaluated in the OCEANIC-AF phase 3 trial for stroke prevention in patients with atrial fibrillation, compared head-to-head against apixaban. This trial was terminated early in August 2024 due to inferior efficacy: asundexian was associated with a higher incidence of stroke or systemic embolism compared to apixaban (1.3% vs. 0.4% per patient-year), despite a favorable bleeding profile [12]. The OCEANIC-AF results highlighted the critical distinction between cardioembolic stroke mechanisms (where FXIa inhibition alone may be insufficient given the dominant contribution of atrial thrombi requiring more complete anticoagulation) and non-cardioembolic stroke mechanisms

(where contact activation and thrombus propagation on atherosclerotic plaques represent more relevant FXIa-dependent pathways). This mechanistic rationale continued to support the OCEANIC-STROKE program.

5. THE OCEANIC-STROKE PHASE 3 TRIAL

OCEANIC-STROKE (Oral faCtor Eleven A iNhibitor asundexian as novel antithrombotic – STROKE; NCT05686070; EudraCT 2022-001949-38) was a phase 3, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial. The study was funded by Bayer AG and coordinated by the Population Health Research Institute (PHRI) at McMaster University/Hamilton Health Sciences, Ontario, Canada. Principal investigators were Dr. Mike Sharma and Dr. Ashkan Shoamanesh of McMaster University/PHRI. The study was conducted across 37 countries, making it one of the largest global cerebrovascular intervention trials ever conducted. The trial was registered in February 2022 and received Fast Track Designation from the U.S. Food and Drug Administration (FDA) in February 2022 specifically for secondary stroke prevention following non cardioembolic ischemic stroke. Between January 2023 and February 2025, 12,327 patients were enrolled and randomized. Primary results were presented at the International Stroke Conference 2026 in New Orleans, Louisiana (February 4–6, 2026) and simultaneously published in the New England Journal of Medicine (April 15, 2026). Eligible patients were adults presenting within 72 hours of the onset of a qualifying non cardioembolic ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤ 15) or high-risk TIA (ABCD2 score of 6 or 7). The non cardioembolic classification required that known sources of cardioembolic stroke (such as atrial fibrillation, recent myocardial infarction, intracardiac thrombus, or significant valvular disease) be excluded—conditions typically treated with full anticoagulation. Patients also required at least one of the following features indicative of large-vessel or atherosclerotic disease: evidence of extra- or intracranial artery atherosclerosis on imaging; a documented history of atherosclerotic disease; or imaging confirmation of an acute non-lacunar cortical infarct. Key exclusion criteria included conditions requiring anticoagulation, active significant non-hemorrhagic infarction-related bleeding (other than hemorrhagic infarction grades HI1 or HI2), or prior stroke with high disability (mRS ≥ 4). Participants were stratified at randomization by planned antiplatelet strategy (single antiplatelet therapy [SAPT] vs. dual antiplatelet therapy [DAPT]).

Table 01: Key Baseline Characteristics of the OCEANIC-STROKE Trial Population

Characteristic	OCEANIC-STROKE (N=12,327)
Total randomized	12,327 (6,162 asundexian; 6,165 placebo)
Enrollment period	January 2023 – February 2025
Countries enrolled	37 countries
Age (mean $\pm$ SD)	68 $\pm$ 11 years
Male sex	67%
Index event: Ischemic stroke	95%
Index event: High-risk TIA (ABCD2 6-7)	5%
Reperfusion therapy (thrombolysis/thrombectomy)	27.4% of stroke patients
TOAST classification – Large artery atherosclerosis	43%
TOAST classification – Small vessel (lacunar)	22%

TOAST classification – Undetermined etiology (ESUS-like)	30%
TOAST classification – Other / cardioembolic	~5%
Randomized to DAPT background	~70%
Randomized to SAPT background	~30%

6. TREATMENT REGIMENS AND FOLLOW-UP

Randomized patients received asundexian 50 mg orally once daily or matching placebo, administered in addition to their planned antiplatelet regimen (determined by the treating physician prior to randomization). DAPT, predominantly aspirin 75–325 mg plus clopidogrel 75 mg daily, was planned for approximately 70% of participants, with the duration determined by standard local practice (typically 21–90 days). SAPT (aspirin alone or clopidogrel alone) was planned for the remaining approximately 30%. Asundexian or placebo was continued throughout the observation period, which was event-driven, targeting a pre-specified number of primary outcome events. The primary efficacy endpoint was time to first occurrence of ischemic stroke (fatal or nonfatal), analyzed using a cause-specific hazard model accounting for the competing risk of death. Secondary efficacy endpoints included: (1) a composite of death from cardiovascular causes, myocardial infarction, or stroke; (2) all stroke (ischemic plus hemorrhagic); (3) TIA; and (4) individual components of the composite secondary endpoint. The primary safety endpoint was ISTH (International Society on Thrombosis and Haemostasias)- defined major bleeding. Secondary safety endpoints encompassed ISTH major or clinically relevant nonmajor bleeding, clinically relevant nonmajor bleeding alone, symptomatic intracranial hemorrhage, hemorrhagic stroke, and fatal bleeding. All events were adjudicated by an independent blinded committee.

7. RESULTS AND DISCUSSION

Among the 12,327 randomized patients (6,162 asundexian; 6,165 placebo), the primary efficacy outcome of ischemic stroke occurred in 6.2% of asundexian-treated patients compared with 8.4% of placebo-treated patients over the observation period. This corresponds to a cause-specific hazard ratio of 0.74 (95% CI, 0.65–0.84; $P < 0.001$), representing a statistically significant and clinically meaningful 26% relative risk reduction in ischemic stroke [13]. The separation of Kaplan-Meier curves between treatment groups was observed early—within the first weeks of treatment—and was maintained throughout the entire follow-up period, suggesting a consistent and durable treatment benefit rather than one limited to the acute post-stroke phase. This early separation is clinically important, given that the risk of recurrent stroke peaks in the days immediately following the index event. The composite secondary endpoint of death from cardiovascular causes, myocardial infarction, or stroke was also significantly lower in the asundexian group compared to placebo, demonstrating a broader cardiovascular benefit beyond stroke prevention alone. The reduction in ischemic stroke was accompanied by consistent numerical trends across secondary cerebrovascular endpoints, further supporting the robustness of the primary efficacy signal.

Table 02: Key Efficacy and Safety Outcomes of the OCEANIC-STROKE Trial

Outcome	Asundexian 50 mg (n=6,162)	Placebo (n=6,165)	csHR (95% CI)	P-value
PRIMARY EFFICACY				
Ischemic stroke	6.2%	8.4%	0.74 (0.65–0.84)	<0.001
SECONDARY EFFICACY				
CV death / MI / Stroke (composite)	Lower	Reference	Favors asundexian	Significant
PRIMARY SAFETY				
ISTH major bleeding	1.9%	1.7%	1.10 (0.85–1.44)	NS
SECONDARY SAFETY				
Symptomatic intracranial hemorrhage	Similar	Similar	—	NS
Fatal bleeding	Similar	Similar	—	NS
TOLERABILITY				
Any adverse event	69.3%	70.1%	—	NS
Serious adverse event	19.2%	19.5%	—	NS

The primary safety endpoint of ISTH major bleeding occurred in 1.9% of patients receiving asundexian compared with 1.7% in the placebo group (csHR, 1.10; 95% CI, 0.85–1.44), a difference that was not statistically significant. This finding is particularly noteworthy: it demonstrates that the 26% reduction in ischemic stroke achieved with asundexian was not accompanied by any clinically meaningful increase in serious hemorrhagic risk—a critical limitation that has historically impeded adoption of anticoagulant therapies in non-cardioembolic stroke. Symmetrically favorable patterns were observed across all secondary safety endpoints. Rates of symptomatic intracranial hemorrhage, hemorrhagic stroke, clinically relevant nonmajor bleeding, and fatal bleeding were all similar between treatment groups. The incidence of any adverse event was 69.3% with asundexian versus 70.1% with placebo; serious adverse events occurred in 19.2% and 19.5% of patients, respectively—demonstrating comparable overall tolerability profiles.

8. SUBGROUP ANALYSES AND CONSISTENCY OF EFFECT

One of the most compelling aspects of the OCEANIC-STROKE results was the consistency of treatment benefit across a broad range of prespecified patient subgroups. Presented in expanded form at the International Stroke Conference 2026, these analyses demonstrated treatment effects favoring asundexian regardless of:

- Sex (male and female): No significant heterogeneity of effect was observed between male and female patients, addressing concerns that antithrombotic efficacy might vary by sex.

- Age: The benefit was consistent across age groups, including elderly patients who represent the majority of the stroke population and who are often considered at higher bleeding risk with antithrombotic agents.
- Use of reperfusion therapy: Among the 27.4% of stroke patients who received thrombolysis and/or mechanical thrombectomy, asundexian's benefit was preserved, indicating no detrimental interaction with acute revascularization treatment.
- Antiplatelet background (DAPT vs. SAPT): Benefit was consistent whether patients received DAPT or SAPT, suggesting that the FXIa inhibition pathway offers complementary protection independent of the degree of antiplatelet coverage.
- TOAST stroke subtype: Among the large subtype cohorts—approximately 5,000 patients with large- artery atherosclerosis (43%), 2,600 with small-vessel occlusion (22%), and 3,500 with undetermined etiology (30%, ESUS-like)—treatment effects favored asundexian across all groups, with numerically the largest relative and absolute risk reductions observed in the undetermined/ESUS-like group (hypothesis-generating).
- Index event (stroke vs. high-risk TIA): Benefit was observed regardless of whether the qualifying event was an ischemic stroke or a high-risk TIA, though the TIA subgroup was smaller.

Importantly, contrary to expectations from phase 2 exploratory analyses that had suggested potential differential effects by stroke subtype (particularly a possible preferential benefit in ESUS-like patients), the phase 3 data did not demonstrate statistically significant heterogeneity of effect across subtypes. The size of the phase 3 subgroups—substantially larger than any prior trial—lent considerable credibility to the conclusion of a broadly generalizable benefit across non cardioembolic stroke [14]. The co-principal investigator Dr. Ashkan Shoamanesh summarized: "The consistent reduction in secondary events with asundexian across all types of strokes included in the trial is particularly striking. OCEANIC-STROKE was deliberately designed to enroll all common stroke subtypes, and it is reassuring that the benefit appears across this diverse population [15]."

9. CONTEXTUALIZING OCEANIC-STROKE WITHIN THE LANDSCAPE OF SECONDARY STROKE PREVENTION TRIALS

The historical standard for secondary prevention after non cardioembolic ischemic stroke has been established through landmark trials including CHANCE (clopidogrel plus aspirin vs. aspirin alone in minor stroke/TIA, demonstrating benefit in a 21-day window), POINT (extended DAPT vs. aspirin alone), and THALES (ticagrelor plus aspirin vs. aspirin alone) [16-18]. These trials established that short-term DAPT (typically 21–90 days) reduces the risk of recurrent stroke compared to aspirin monotherapy, particularly in the highest-risk early period. However, extended DAPT beyond this window does not provide additional benefit and increases major bleeding risk, leaving patients on long-term SAPT with residual high stroke recurrence rates. Multiple trials have investigated conventional anticoagulants (warfarin, DOACs) in non-cardioembolic stroke settings, uniformly failing to demonstrate net clinical benefit due to excess hemorrhagic risk. The WARSS trial found no significant benefit of warfarin over aspirin in non-cardioembolic stroke. The NAVIGATE-ESUS and RESPECT-ESUS trials both failed to show superiority of rivaroxaban or dabigatran, respectively, over aspirin for stroke prevention in embolic stroke of undetermined source, with excess bleeding offsetting any thrombotic benefit [19,20]. These failures highlighted the need for agents

that could provide anticoagulant-level efficacy with antiplatelet-level or lower bleeding risk—precisely the niche that factor X_{II}a inhibitors were designed to occupy. Asundexian is not the only FX_{II}a inhibitor in development for secondary stroke prevention. Milvexian (Bristol Myers Squibb/Janssen), another oral small-molecule FX_{II}a inhibitor, was evaluated in the phase 2 AXIOMATIC-SSP trial in patients with recent ischemic stroke or TIA, demonstrating dose-dependent reductions in symptomatic ischemic stroke without significantly increased bleeding at most doses [21]. Milvexian is being evaluated in the ongoing phase 3 LIBREXIA-STROKE trial. The emergence of two agents targeting the same pathway in the same indication provides important convergent validation of FX_{II}a as a genuine therapeutic target. Additionally, monoclonal antibody FX_{II} inhibitors (e.g., abelacimab) are in various stages of clinical evaluation, though their route of administration (subcutaneous injection) differs from the oral route of small-molecule FX_{II}a inhibitors [22].

10. CLINICAL IMPLICATIONS

OCEANIC-STROKE marks the first successful phase 3 trial of a factor X_{II}a inhibitor for secondary stroke prevention and the first phase 3 trial in this setting to achieve both a significant reduction in recurrent ischemic stroke and a non-significant increase in major bleeding. Principal investigator Dr. Mike Sharma described the result as representing "a major step toward safer and more effective long-term treatment for stroke prevention," noting that it achieves what researchers have sought for decades—a durable antithrombotic therapy without the bleeding penalty [23]. The significance is amplified by the magnitude and consistency of effect. A 26% relative risk reduction translates to a meaningful absolute risk reduction of 2.2 percentage points (8.4% to 6.2%) over the trial period, which, given the high baseline stroke recurrence rates in this population, represents a substantial clinical benefit. When applied across the millions of patients surviving ischemic stroke annually worldwide, this could translate to hundreds of thousands of prevented recurrent strokes globally [24]. A critical clinical implication of asundexian's profile is the potential for long-term administration. Unlike DAPT, which is restricted to the early post-stroke window due to cumulative bleeding risk, asundexian's lack of significant major bleeding increase in OCEANIC-STROKE suggests it could be maintained as a long-term therapy—addressing the unmet need for sustained secondary prevention beyond the initial high-risk period. The sustained separation of Kaplan-Meier efficacy curves throughout the observation period supports continued benefit over time, without evidence of attenuation of effect [25].

11. PATIENT SELECTION AND PRACTICAL CONSIDERATIONS

The broad eligibility criteria of OCEANIC-STROKE—encompassing large artery atherosclerosis, small vessel disease, and undetermined etiology subtypes—mean that the trial results are potentially applicable to the majority of non-cardioembolic stroke patients encountered in clinical practice. The consistency of benefit across DAPT and SAPT backgrounds is particularly practical, as it suggests asundexian may be added regardless of whether the treating clinician opts for mono- or dual antiplatelet therapy. Practical considerations for implementation will include regulatory approval (Bayer is anticipated to pursue approval across major markets, leveraging the FDA Fast Track Designation), access and cost, and integration into existing stroke prevention guidelines. The once-daily oral formulation and the absence of routine coagulation monitoring requirements (unlike warfarin) are significant advantages for real-world adoption. Despite the landmark results of OCEANIC-STROKE, several important questions remain. First, the differential benefit observed numerically in ESUS-like (stroke of undetermined etiology) patients warrants further prospective evaluation. If asundexian provides disproportionate benefit in cryptogenic/ESUS

stroke— possibly related to micro embolic or covert cardiac mechanisms—dedicated trials or subgroup-targeted analyses could refine patient selection. Second, the long-term safety profile beyond the OCEANIC-STROKE observation period requires characterization through post-marketing surveillance. Third, the optimal sequencing of asundexian with DAPT and the timing of transition from DAPT to SAPT plus asundexian needs clarification. Fourth, the role of asundexian in patients who are anticoagulation-ineligible with atrial fibrillation (the OCEANIC-AFINA program, which was under re-evaluation) remains an area of ongoing scientific interest. Several limitations of OCEANIC-STROKE merit consideration. First, as a placebo-controlled trial, it does not directly compare asundexian to other active antithrombotic strategies beyond the background antiplatelet therapy. Whether asundexian is superior or non-inferior to alternative approaches (e.g., extended DAPT, ticagrelor monotherapy) remains unknown. Second, the trial design excluded patients requiring anticoagulation for detected cardioembolic sources, limiting generalizability to that population. Third, while the trial enrolled a large international population across 37 countries, geographic and racial/ethnic diversity in subgroup analyses has not been fully published at the time of this review. Fourth, the event-driven design means that individual patient follow-up duration varied, and the absolute rate data reflect event incidence across differing exposure windows. Fifth, Bayer's funding role in trial design and analysis, while common in industry-sponsored phase 3 trials, should be acknowledged in the context of critical appraisal.

12. CONCLUSIONS

Asundexian represents a major advance in the secondary prevention of ischemic stroke. The OCEANIC-STROKE phase 3 trial conclusively demonstrates that once-daily asundexian 50 mg, administered in addition to standard antiplatelet therapy in patients with recent non cardioembolic ischemic stroke or high-risk TIA, reduces the risk of recurrent ischemic stroke by 26% compared to placebo, without increasing the risk of major bleeding. These results are consistent across diverse patient subgroups defined by age, sex, stroke subtype, reperfusion therapy, and antiplatelet background. This outcome fulfills a long-standing therapeutic aspiration in stroke neurology: an antithrombotic agent capable of providing sustained, meaningful risk reduction in non-cardioembolic stroke without the hemorrhagic trade-off that has historically limited anticoagulant use in this population. OCEANIC-STROKE is the first phase 3 study of a factor XIa inhibitor to achieve this goal, vindicating the biological hypothesis that FXIa inhibition can selectively target pathological thrombosis while preserving hemostasis. As asundexian proceeds through the regulatory process toward potential approval, it has the capacity to reshape secondary stroke prevention guidelines globally and provide clinicians with a new, effective, and well-tolerated tool for one of the most challenging problems in cerebrovascular medicine. Further research to optimize patient selection, define long-term safety, and characterize benefit in specific subpopulations will continue to refine the role of this agent in clinical practice.

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