Journal of Drug Discovery and Clinical Research
Content Available at www.lapinpress.com ISSN (O): 3139-8170
(An online peer reviewed Referred Journal)

Review Article
OPEN ACCESS

ASUNDEXIAN: A REVIEW OF COMPARATIVE CLINICAL STUDIES, THERAPEUTIC POTENTIAL, AND FUTURE PERSPECTIVES STUDIES.

SADE TULASI CHANDRIKA[1], SANGINEEDI INDU HARINI[*2]

[1]*Research Scholar, Koringa college of Pharmacy, Korangi.*
[2]*Assitant Professor, Koringa College of Pharmacy, Koringi, Kakinada.*

***Corresponding Author**
Dr. Sangineedi Induharini

DOI: https://doi.org/10.70604/jddcr.v1i2.239

Article History: Received: 16 Aug 2026, Revised: 04 Oct 2026, Accepted: 28 Oct 2026

Abstract: Asundexian is an investigational oral anticoagulant that selectively inhibits activated coagulation factor XIa (FXIa). It represents a novel approach to thromboembolic disease prevention by targeting the intrinsic coagulation pathway while potentially preserving physiological haemostasis. Unlike conventional anticoagulants, such as warfarin and direct oral anticoagulants (DOACs), which target vitamin K-dependent coagulation factors or factor Xa and thrombin, asundexian selectively inhibits factor XIa.This review discusses the pharmacological properties, mechanism of action, clinical efficacy, safety profile, and comparative clinical studies of asundexian. Particular attention is given to comparisons with apixaban and other anticoagulant therapies, including studies evaluating stroke prevention and bleeding outcomes. The clinical development of asundexian has provided important insights into the potential benefits and limitations of factor XIa inhibition. Its future therapeutic role may involve patients with non-cardioembolic ischaemic stroke and other thromboembolic conditions where reducing bleeding complications is an important treatment objective. Further large-scale clinical trials are necessary to establish its long-term efficacy, safety, appropriate indications, and position in clinical practice.

Keywords: *Asundexian, Factor XIa inhibitor, Anticoagulants, Apixaban, Thromboembolism, Ischaemic stroke, Clinical trials, Future perspectives.*

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INTRODUCTION

Thromboembolic disorders are major causes of morbidity and mortality worldwide. Anticoagulants play an essential role in preventing and treating conditions such as atrial fibrillation-associated stroke, venous thromboembolism, and recurrent ischaemic events.Currently available anticoagulants include vitamin K antagonists, direct thrombin inhibitors, and direct factor Xa inhibitors. Although these medications are effective, their anticoagulant activity can increase the risk of bleeding, particularly gastrointestinal and intracranial haemorrhage.Asundexian is a novel, orally administered, selective factor XIa inhibitor developed to provide antithrombotic protection with potentially reduced bleeding risk. By selectively inhibiting factor XIa, it aims to interfere with pathological thrombus formation while having a relatively limited effect on normal haemostatic mechanisms.The development of asundexian represents an important advancement in anticoagulant research and provides an opportunity to explore a new therapeutic target in cardiovascular medicine.

2. MECHANISM OF ACTION

Asundexian selectively inhibits activated factor XI (FXIa), an important enzyme involved in the intrinsic coagulation pathway.

The mechanism involves:

1. Factor XI is activated to factor XIa during the coagulation process.
2. Factor XIa activates factor IX to factor IXa.
3. Factor IXa participates in the activation of factor X through the intrinsic tenase complex.
4. Activated factor X promotes thrombin generation and subsequent fibrin formation.
5. Asundexian inhibits factor XIa, reducing downstream coagulation activity and pathological thrombus formation.

The selective inhibition of factor XIa may reduce thrombus formation without producing the same degree of interference with haemostasis as conventional anticoagulants. However, this proposed bleeding advantage must be evaluated separately for each clinical indication.

3. PHARMACOLOGICAL PROPERTIES

Table 01: Pharmacological Profile of Asundexian

Property	Description
Drug name	Asundexian
Drug class	Direct factor XIa inhibitor
Administration	Oral
Target	Activated factor XI (FXIa)
Mechanism	Selective inhibition of FXIa
Therapeutic objective	Prevention of thromboembolic events
Development status	Investigational; clinical development indication-dependent

4. Comparative clinical studies of asundexian:

Clinical trials have evaluated asundexian against placebo and established anticoagulants to determine its efficacy, safety, and therapeutic advantages.

The major studies include PACIFIC-AF, PACIFIC-STROKE, OCEANIC-AF, and OCEANIC-STROKE.

5. Comparative analysis of major clinical trials:

The following table summarizes the important clinical studies of asundexian.

Table 02: Summary of Major Clinical Trials Evaluating Asundexian in Thromboembolic Prevention

Clinical trial	Phase	Comparator	Major outcome
PACIFIC-AF	II	Apixaban	Lower bleeding with asundexian
PACIFIC-STROKE	IIb	Placebo	No significant primary efficacy benefit
OCEANIC-AF	III	Apixaban	Inferior stroke prevention; less bleeding
OCEANIC-STROKE	III	Placebo + antiplatelet therapy	Significant reduction in recurrent ischaemic stroke

5.1 Comparison of asundexian with other anticoagulants:

Pharmacological and clinical comparison

Table 03: Comparative Pharmacological Characteristics, Clinical Evidence, and Limitations of Asundexian and Established Oral Anticoagulants

Parameter	Asundexian	Apixaban	Rivaroxaban	Warfarin
Drug class	FXIa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Vitamin K antagonist
Target	Factor Xia	Factor Xa	Factor Xa	Vitamin K-dependent factors
Administration	Oral	Oral	Oral	Oral
Monitoring	No routine INR monitoring	No routine INR monitoring	No routine INR monitoring	INR monitoring required
Clinical evidence	Strong Phase III evidence in secondary non-cardioembolic stroke prevention	Established evidence in AF	Established evidence in several thromboembolic indications	Established anticoagulant
Major limitation	Not effective enough compared with apixaban in OCEANIC-AF	Bleeding risk	Bleeding risk	Variable response and dietary interactions

Interpretation: Asundexian has a different mechanism of action from conventional anticoagulants. Its clinical value is not based on replacing all existing anticoagulants, but on potentially providing an additional treatment option in selected patients, particularly those requiring secondary prevention after non-cardioembolic ischaemic stroke.

5.2 Comparison with other investigational factor XI inhibitors:

Other drugs targeting factor XI or factor XIa are also under clinical investigation.

1. Milvexian

An oral factor XIa inhibitor being investigated for prevention of thromboembolic events. The LIBREXIA-STROKE Phase III programme evaluates its role in patients with acute ischaemic stroke or high-risk TIA.

2. Abelacimab

A monoclonal antibody that targets factor XI and prevents its activation. It is administered by subcutaneous injection and has been studied in patients with atrial fibrillation.

Comparison: Asundexian and milvexian are oral small-molecule inhibitors of factor XIa, whereas abelacimab is a monoclonal antibody targeting factor XI. These drugs differ in their pharmacological mechanisms, administration routes, and clinical development programmes. Direct comparative trials are required before their relative clinical effectiveness can be established.

6. ADVANTAGES OF ASUNDEXIAN:

The potential advantages of asundexian include:

1. Selective mechanism: It selectively inhibits factor XIa rather than broadly suppressing coagulation.
2. Oral administration: It offers convenient once-daily oral administration.
3. Potential bleeding advantage: Its mechanism may reduce the risk of major bleeding compared with conventional anticoagulants in appropriate clinical settings.
4. Targeted thrombus prevention: It may help reduce pathological clot formation.
5. Combination therapy: It has demonstrated efficacy when administered alongside antiplatelet therapy in secondary stroke prevention.
6. Novel therapeutic target: It provides an alternative pharmacological approach to conventional anticoagulation.

7. LIMITATIONS AND CHALLENGES

Despite promising clinical results, several limitations should be considered.

- Its efficacy is indication-dependent.
- OCEANIC-AF demonstrated inadequate thromboembolic protection compared with apixaban.
- Long-term safety data require continued evaluation.
- The possibility of bleeding remains, particularly when combined with antiplatelet agents.
- Its efficacy in different patient populations requires further investigation.
- The optimal duration of treatment and appropriate patient selection need to be established.

8. FUTURE PERSPECTIVES OF ASUNDEXIAN:

Asundexian has emerged as an important drug candidate in the development of next-generation antithrombotic therapy. The positive findings from OCEANIC-STROKE have increased interest in factor XIa inhibition as a therapeutic strategy for preventing recurrent ischaemic stroke.

The following areas represent important future research directions.

8.1 Secondary prevention of ischaemic stroke:

The most promising future application of asundexian is the prevention of recurrent non-cardioembolic ischaemic stroke.

OCEANIC-STROKE demonstrated a 26% relative reduction in recurrent ischaemic stroke compared with placebo when added to standard antiplatelet treatment. Further studies may help determine its long-term benefits in different stroke subtypes.

8.2 Development of safer anticoagulant therapy:

One of the major objectives of anticoagulant research is to reduce thromboembolic events without increasing bleeding complications. Asundexian may contribute to this objective through selective inhibition of factor XIa. Future investigations should evaluate its safety in elderly patients and individuals with an increased risk of bleeding.

8.3 Application in cardiovascular diseases:

Further research may investigate factor XIa inhibition in:

- Coronary artery disease.
- Peripheral arterial disease.
- Recurrent thromboembolic disorders.
- Patients with atherosclerotic cardiovascular disease.

However, efficacy in these conditions cannot be assumed from the positive stroke trial results and requires dedicated clinical studies.

8.4 Combination with antiplatelet drugs:

The OCEANIC-STROKE findings provide evidence supporting the combination of asundexian with single or dual antiplatelet therapy in selected patients.

Future studies should establish the optimal combination, duration of treatment, and bleeding-risk profile.

8.5 Individualized treatment approaches:

Future research may explore patient-specific factors such as:

- Age and renal function.
- Previous bleeding history.
- Stroke subtype.
- Genetic variations associated with coagulation.
- Degree of factor XIa inhibition.

These investigations may help identify patients most likely to benefit from treatment.

8.6 Regulatory development and clinical availability:

An important development occurred on 26 October 2026, when China's National Medical Products Administration approved asundexian 50 mg under the brand name Sunharbo for reducing stroke risk in adults following non-cardioembolic ischaemic stroke or high-risk TIA.

In the United States, the FDA accepted Bayer's application and granted Priority Review in May 2026. Regulatory applications in other markets are also under evaluation.

9. FUTURE RESEARCH RECOMMENDATIONS

The following studies would strengthen the clinical evidence for asundexian:

Table 04: Future Research Directions and Perspectives for the Clinical Development of Asundexian

Research area	Future objective
Long-term clinical trials	Evaluate long-term efficacy and safety
Dose optimization	Identify the optimal therapeutic dose
Elderly population	Assess efficacy and bleeding risk in older patients

Renal impairment	Evaluate pharmacokinetics and safety
Combination therapy	Determine optimal use with antiplatelet agents
Comparative trials	Compare with other factor XIa inhibitors
Real-world studies	Evaluate effectiveness in routine clinical practice
Indian population studies	Assess efficacy, safety and cost-effectiveness in Indian patients

10. CONCLUSION

Asundexian represents an important advancement in the development of selective anticoagulant therapy through inhibition of activated factor XIa. Its mechanism of action offers a different approach to preventing pathological thrombus formation, with the potential advantage of reducing bleeding complications.Comparative clinical studies have demonstrated both the advantages and limitations of this drug. PACIFIC-AF showed a favourable bleeding profile compared with apixaban, whereas OCEANIC-AF demonstrated that asundexian did not provide adequate protection against stroke and systemic embolism in patients with atrial fibrillation. In contrast, OCEANIC-STROKE demonstrated significant efficacy in reducing recurrent ischaemic stroke among patients with non-cardioembolic stroke or high-risk TIA when added to antiplatelet therapy, without a statistically significant increase in major bleeding.The approval of asundexian in China in October 2026 represents an important milestone in its clinical development. Further research should focus on long-term safety, comparative effectiveness, optimal patient selection, and its potential role in other cardiovascular and thromboembolic conditions. Overall, asundexian has promising therapeutic potential, particularly in secondary prevention of non-cardioembolic ischaemic stroke. However, its clinical application should be guided by indication-specific evidence rather than assuming that it can replace conventional anticoagulants in all patients.

11. FUNDING

Nil

12. ACKNOWLEDGEMENT

Not Declared.

13. CONFLICT OF INTEREST

Nil

14. INFORMED CONSENT

Not applicable

15. ETHICAL STATEMENT

Not Applicable.

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