McMaster University

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

International Stroke Conference

FACTOR XIa INHIBITION WITH ASUNDEXIAN IN ACUTE NON-CARDIOEMBOLIC STROKE OR HIGH-RISK TRANSIENT ISCHEMIC ATTACK: PRIMARY RESULTS OF THE OCEANIC-STROKE TRIAL

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American Stroke Association.
A division of the American Heart Association.

DISCLOSURES

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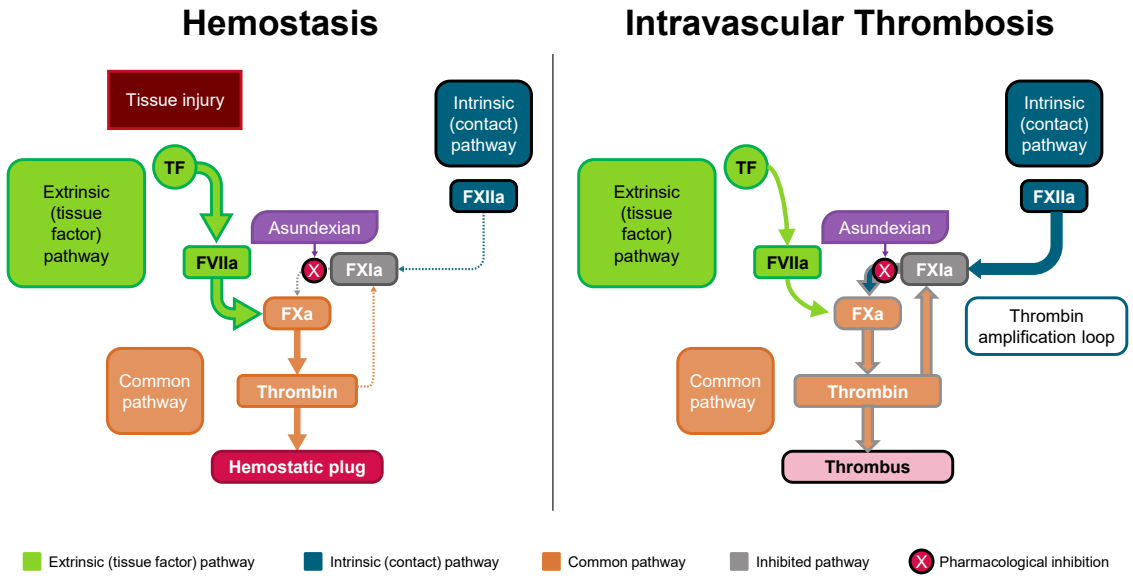
BACKGROUND

- Genetic FXI deficiency associated with:
  - reduced risk of ischemic stroke
  - without increased risk of ICH[1–3]
- FXI has a minor role in hemostasis but may increase pathologic thrombosis
- Potential to uncouple hemostasis from thrombosis makes FXIa an attractive therapeutic target



Dashed arrows indicate minimal involvement of FXIa in hemostasis.
Figure adapted from Sharma M, et al. *European Stroke Journal.* 2026;11(1):aakaf017.

FVIIa, activated Factor VII; FXa, activated Factor X; FXI, Factor XI; FXIa, activated Factor XI; FXIIa, activated Factor XII; ICH, intracerebral hemorrhage; TF, tissue factor.

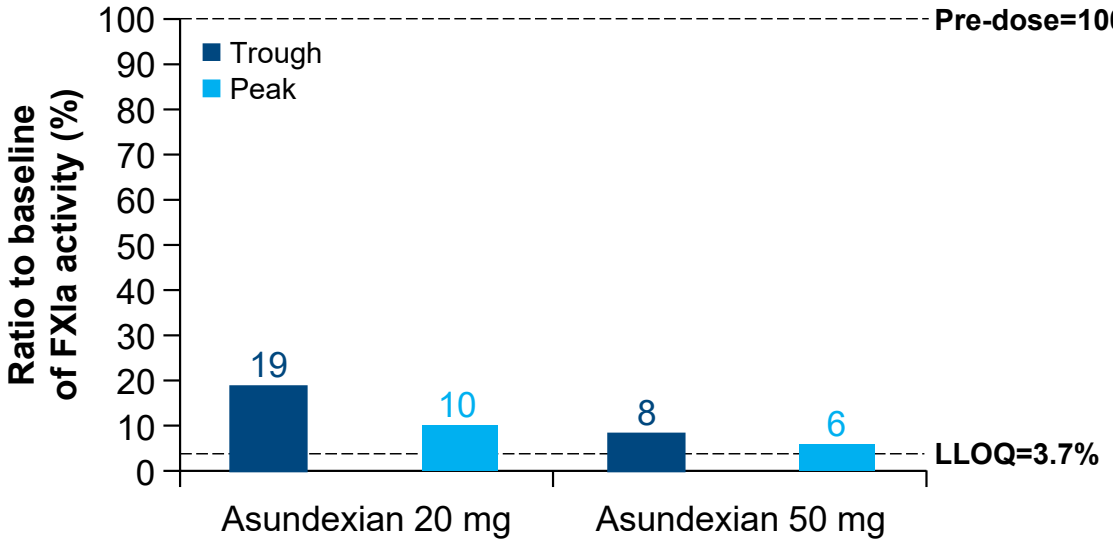
1. Gill D, et al. *Stroke*. 2018;49(11):2761–3; 2. Salomon O, et al. *Blood.* 2008;111(8):4113–7; 3. Georgi B, et al. *Stroke*. 2019;50(11):3004–12.

ASUNDEXIAN

- Direct oral inhibitor of FXIa[1,2]
  - Once daily dosing
- No effect on bleeding time – alone or with DAPT
- Phase 2 studies >4000 participants showed[3–6]
  - >90% inhibition of FXIa at peak and trough
  - No significant increase in major bleeding over placebo with or without antiplatelets

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators*



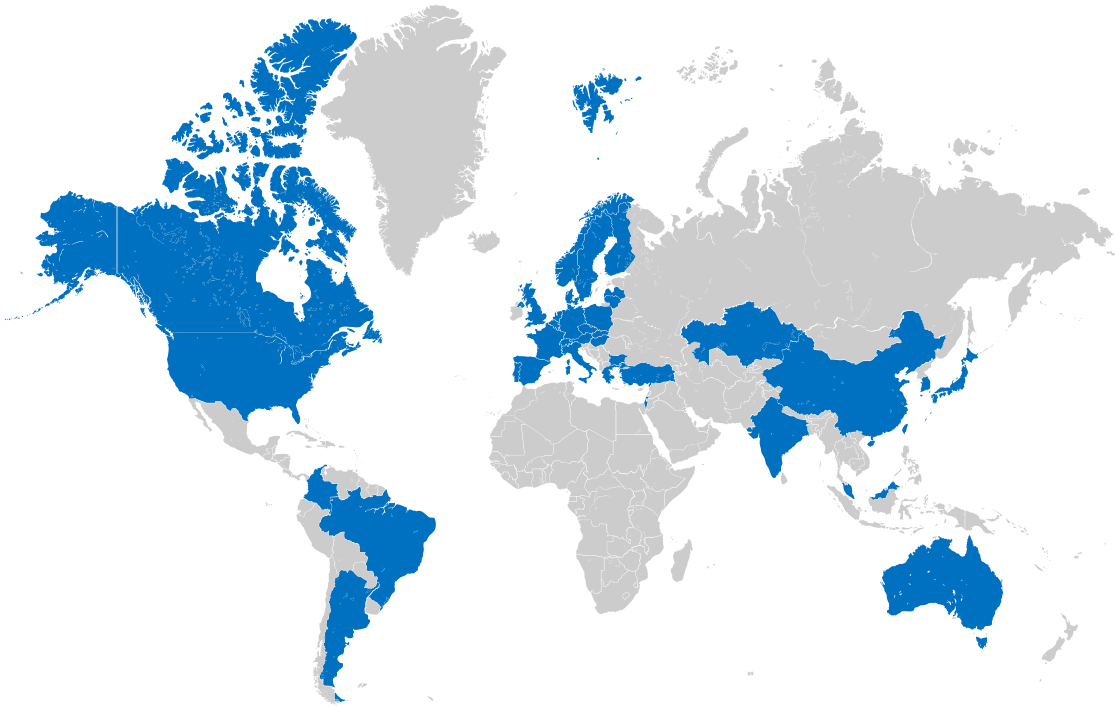
DAPT, dual antiplatelet therapy; FXIa, activated Factor XI.

1. Heitmeier S, et al. *J Thromb Haemost.* 2022;20(6):1400–11; 2. Piel I, et al. *Eur J Drug Metab Pharmacokinet.* 2023;48(4):411–25;
3. Rao SV, et al. *Circulation.* 2022;146(16):1196–206; 4. Piccini JP, et al. *Lancet.* 2022;399(10333):1383–90;
5. Shoamanesh A, et al. *Lancet.* 2022;400(10357):997–1007; 6. Eikelboom JW, et al. *J Am Coll Cardiol.* 2024;83(6):669–78.

OCEANIC-STROKE

Design

- OCEANIC-STROKE
  - Placebo-controlled
  - Double-blinded
  - Event-driven Phase 3 RCT
- Comparing asundexian 50 mg once daily and placebo
- Patients with non-cardioembolic stroke or high-risk TIA
  - Planned for antiplatelet therapy – single or aspirin + P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel)



37 Countries/Regions, 702 Sites

P2Y12, purinergic receptor Y12; RCT, randomized controlled trial; TIA, transient ischemic attack.

OCEANIC-STROKE: KEY ENDPOINTS

Endpoints (time to first occurrence)	
Primary efficacy*	**Primary safety**
Ischemic stroke	ISTH major bleeding
Secondary efficacy*	**Secondary safety**
• All strokes (ischemic and hemorrhagic) • Composite of CV death, MI or stroke • Composite of all-cause mortality, MI or stroke • Ischemic stroke in the first 90 days • Disabling stroke (mRS ≥3 at 90 days)	• Composite of ISTH major or CRNM bleeding • ISTH CRNM bleeding • Symptomatic intracranial hemorrhage • Hemorrhagic stroke • Fatal bleeding • Minor bleeding

*Hypothesis testing conducted using strict hierarchy order for efficacy endpoints.
CRNM, clinically relevant non-major; CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; mRS, modified Rankin score.

KEY INCLUSION AND EXCLUSION CRITERIA

Key inclusion:

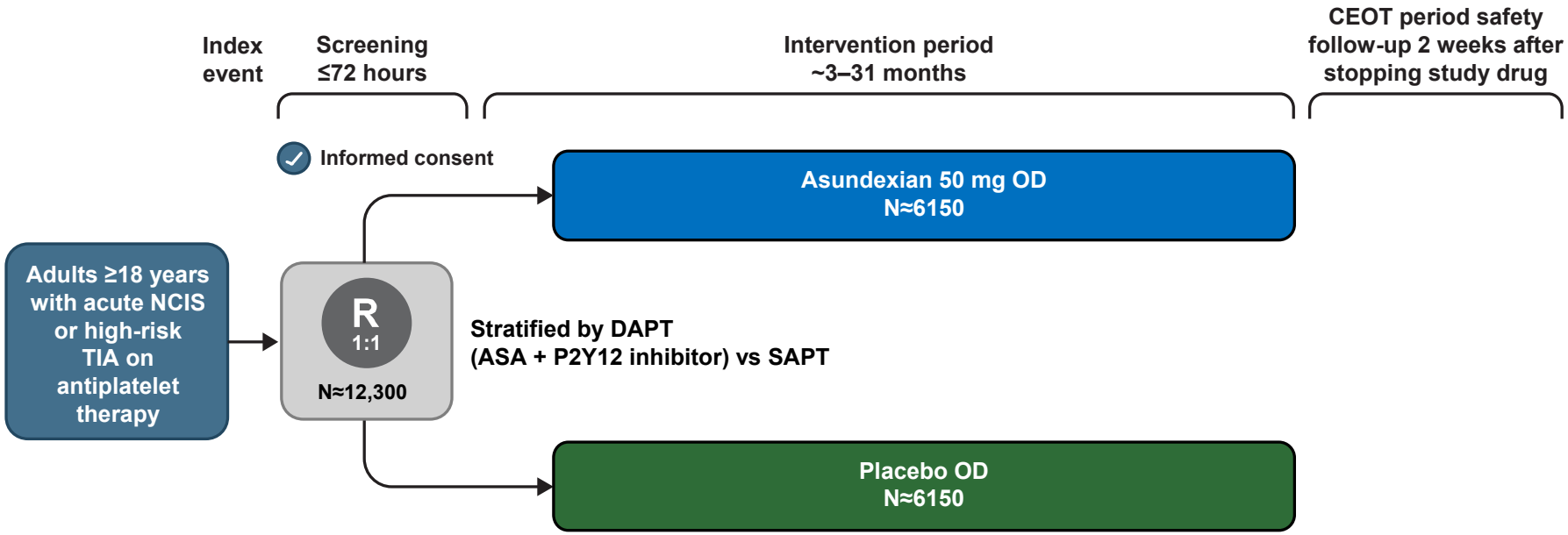
- Participants aged ≥18 years, within 72 hours of symptom onset:
  - Non-cardioembolic ischemic stroke (NIHSS ≤15) **or** high-risk TIA ($ABCD^2$ 6 or 7)
  - History of atherosclerosis **or** evidence of plaque on imaging **or** non-lacunar stroke on imaging
  - Plan for antiplatelet therapy, single or dual

Key exclusion:

- History of AF or other cardioembolic source requiring anticoagulation
- Ischemic stroke within 7 days of index event
- Strokes following procedures (TAVI, CABG) or other specific cause (e.g. vasculitis)
- End-stage renal disease requiring dialysis
- Active non-trivial bleeding (e.g. PH1 or PH2); asymptomatic HT and CMB permitted
- History of non-traumatic ICH; significant GI bleeding within 6 months

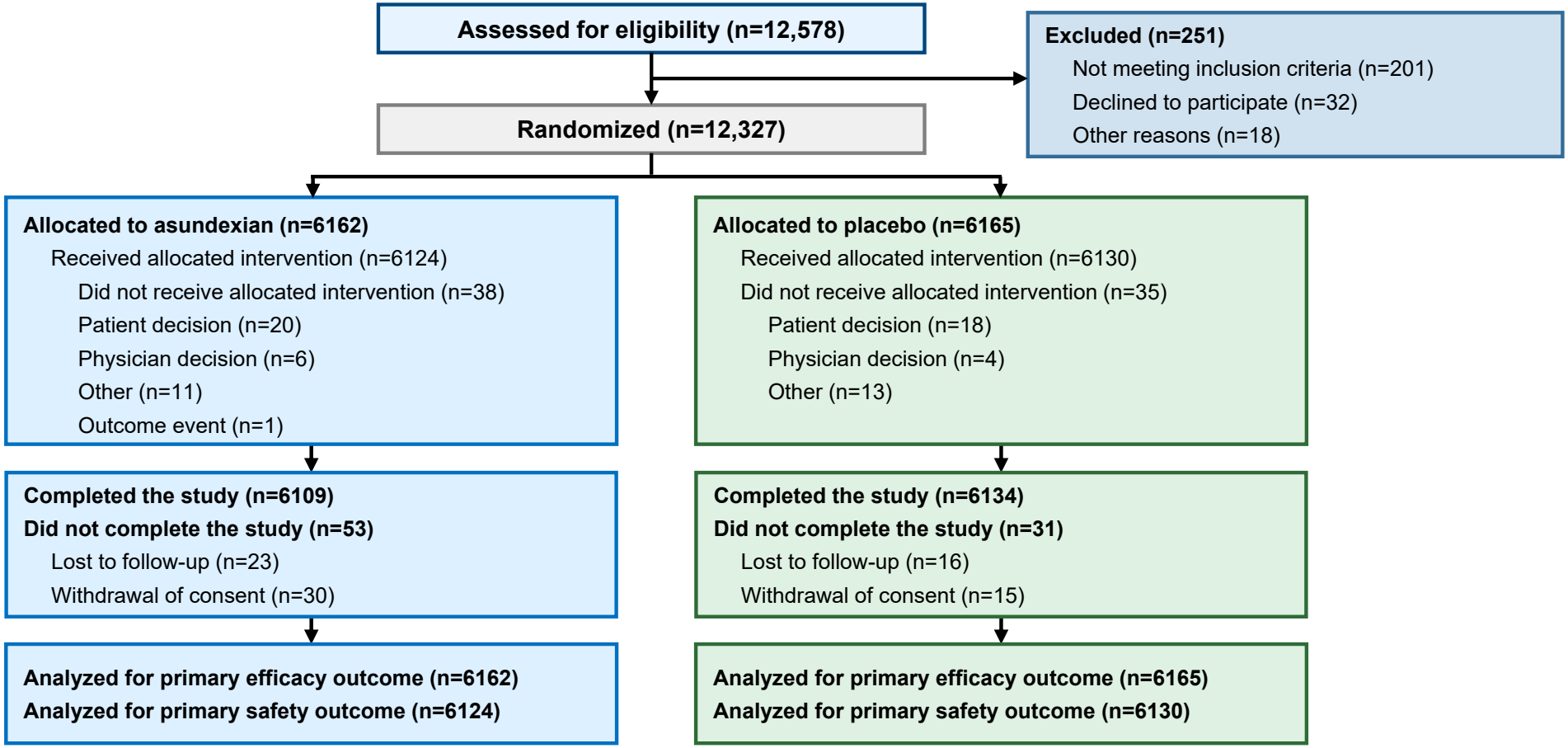
$ABCD^2$, age, blood pressure, clinical features, duration of symptoms, and diabetes; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CMB, cerebral microbleed; GI, gastrointestinal; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

OCEANIC-STROKE: STUDY DESIGN



ASA, aspirin; CEOT, common end of treatment; DAPT, dual antiplatelet therapy; NCIS, non-cardioembolic ischemic stroke; OD, once daily; P2Y12, purinergic receptor Y12; R, randomization; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.
Sharma M, et al. *Eur Stroke J.* 2026;11(1):aakaf017.

CONSORT DIAGRAM



BASELINE CHARACTERISTICS

Characteristics	Asundexian 50 mg	Placebo
Randomized, N	6162	6165
Age, years, mean (SD)	67.7 (10.8)	67.5 (10.9)
Female sex, n (%)	2063 (33.5)	2047 (33.2)
Medical history, n (%)		
Previous history of stroke or TIA	1310 (21.3)	1345 (21.8)
Coronary artery disease	949 (15.4)	1013 (16.4)
Hypertension	4937 (80.1)	4868 (79.0)
Diabetes mellitus	2134 (34.6)	2115 (34.3)
Current smoker	1644 (26.7)	1665 (27.0)
Race, n (%)		
White	4105 (66.6)	4078 (66.1)
Asian	1721 (27.9)	1742 (28.3)
Black	143 (2.3)	139 (2.3)
Other	193 (3.1)	206 (3.3)

SD, standard deviation; TIA, transient ischemic attack.

INDEX EVENT CHARACTERISTICS

Characteristics	Asundexian 50 mg	Placebo
Index event, n (%)		
Ischemic stroke	5839 (94.8)	5838 (94.7)
High-risk TIA	323 (5.2)	325 (5.3)
TOAST subtype of index event,† n (%)		
Large-artery atherosclerosis	2512 (43.0)	2484 (42.5)
Stroke of undetermined etiology	1786 (30.6)	1710 (29.3)
Small-vessel occlusion	1290 (22.1)	1349 (23.1)
Stroke of other etiology	161 (2.8)	188 (3.2)
Cardioembolic	89 (1.5)	107 (1.8)
NIHSS at randomization,† median (IQR)	2 (1, 4)	2 (1, 4)
NIHSS at randomization,† n (%)		
≤3	4087 (70.0)	4079 (69.9)
4–7	1385 (23.7)	1375 (23.6)
≥8	365 (6.3)	382 (6.5)
Dual antiplatelet therapy	3859 (62.6)	3853 (62.5)

†Stroke index event only.
IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

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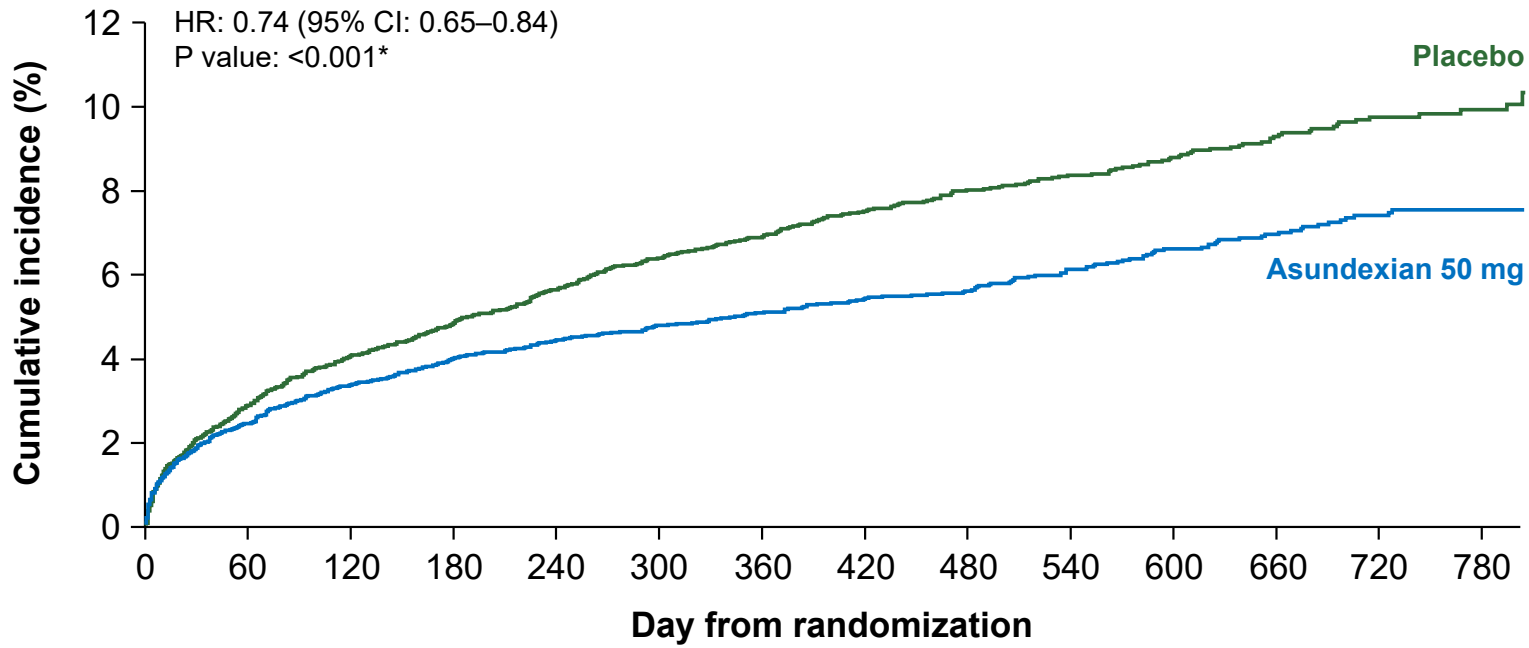
ACUTE TREATMENT OF INDEX STROKE

	Overall N=11677	Asundexian 50 mg N=5839	Placebo N=5838
Intravenous thrombolysis and/or endovascular therapy,† n (%)	3201 (27.4)	1608 (27.5)	1593 (27.3)
Intravenous thrombolysis only	2314 (19.8)	1146 (19.6)	1168 (20.0)
Endovascular therapy only	371 (3.2)	202 (3.5)	169 (2.9)
Intravenous thrombolysis and endovascular therapy	516 (4.4)	260 (4.5)	256 (4.4)

†Stroke index event only.

CUMULATIVE INCIDENCE OF ISCHEMIC STROKE



No. at risk													
Placebo	6165	5949	5853	5754	5370	4840	4406	3990	3497	3070	2564	1961	1410	792
Asundexian 50 mg	6162	5958	5859	5763	5384	4876	4463	4033	3543	3101	2588	2004	1428	810

*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here.
Absolute risk reduction at 1 year was 1.9%, with a number needed to treat of 54.
Cumulative incidence curves are estimated by Aalen–Johansen method, truncated at Day 820.
CI, confidence interval; csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; HR, hazard ratio.

EFFICACY OUTCOMES

Outcome	Asundexian 50 mg (N=6162) n (%)	Placebo (N=6165) n (%)	csHR (95% CI)†	P value‡
Primary efficacy event				
Ischemic stroke	384 (6.2)	518 (8.4)	0.74 (0.65–0.84)	<0.001
Secondary efficacy events				
All strokes (ischemic, hemorrhagic)	404 (6.6)	545 (8.8)	0.74 (0.65–0.84)	<0.001
CV death, MI or stroke	568 (9.2)	685 (11.1)	0.83 (0.74–0.92)	<0.001
All-cause mortality, MI, or stroke	649 (10.5)	757 (12.3)	0.85 (0.77–0.95)	0.003
Ischemic stroke in the first 90 days	183 (3.0)	218 (3.5)	0.84 (0.69–1.02)	0.08
Disabling/fatal stroke¶	128 (2.1)	185 (3.0)	0.69 (0.55–0.87)	Not applicable

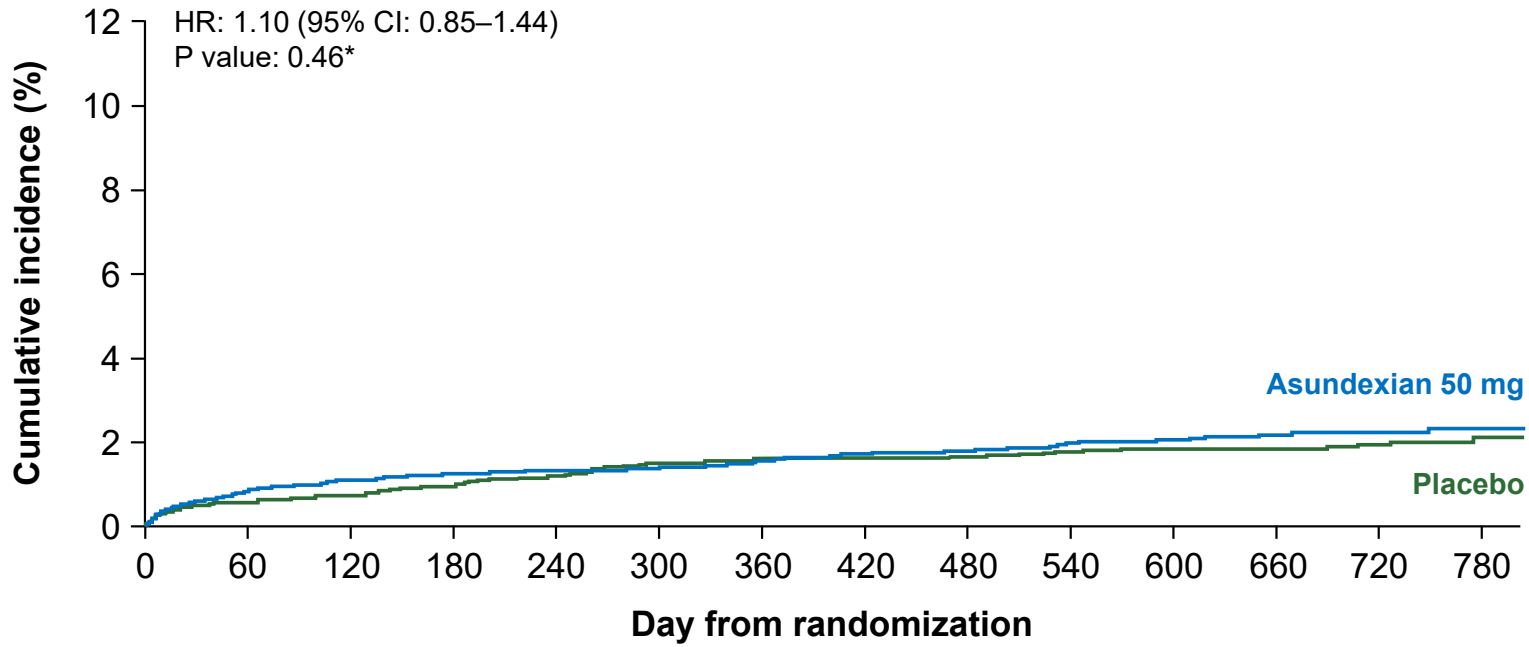
†csHRs are estimated from stratified cox proportional hazard model (stratified by baseline intention of T); ‡P values are obtained from stratified log-rank test (stratified by baseline intention of T); ¶A disabling stroke is defined as a stroke of any type during the trial associated with a modified Rankin Scale (mRS) of ≥3 at 90 days after the stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥3.
csHR, cause-specific hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; mRS, modified Rankin score.

SAFETY OUTCOMES

Outcome	Asundexian 50 mg (N=6162) n (%)	Placebo (N=6165) n (%)	csHR (95% CI)†
Primary safety event			
ISTH major bleeding	117 (1.9)	107 (1.7)	1.10 (0.85–1.44)
Secondary safety events			
ISTH major or clinically relevant non-major bleed	339 (5.5)	307 (5.0)	1.12 (0.96–1.30)
Clinically relevant non-major bleeding	231 (3.8)	210 (3.4)	1.11 (0.92–1.34)
Symptomatic intracranial hemorrhage (includes intracerebral hemorrhage)	41 (0.7)	36 (0.6)	1.15 (0.74–1.80)
Hemorrhagic stroke	13 (0.2)	20 (0.3)	0.66 (0.33–1.32)
Fatal bleeding	14 (0.2)	8 (0.1)	1.77 (0.74–4.23)
Minor bleeding	479 (7.8)	512 (8.4)	0.94 (0.83–1.07)

†csHRs are estimated from stratified Cox proportional hazards model (stratified by baseline intention of DAPT).
CI, confidence interval; csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; ISTH, International Society on Thrombosis and Haemostasis.

CUMULATIVE INCIDENCE OF ISTH MAJOR BLEEDING

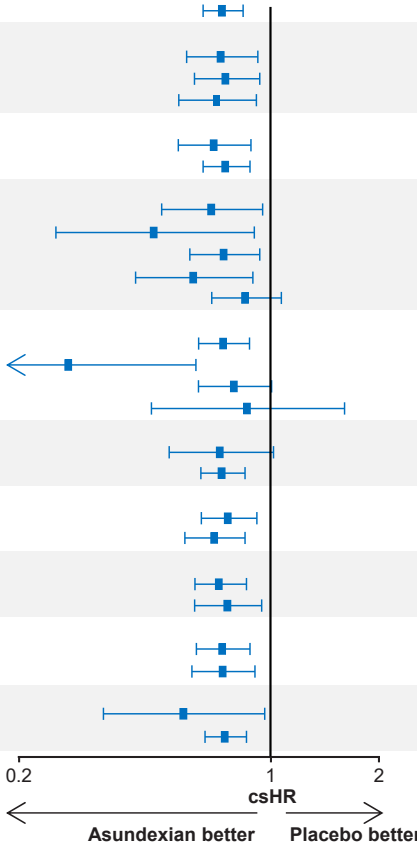


No. at risk														
Placebo	6130	5391	5021	4833	4415	3944	3572	3165	2775	2441	2026	1549	1121	618
Asundexian 50 mg	6124	5354	4968	4807	4366	3900	3547	3104	2699	2374	1943	1508	1082	613

*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here.
Cumulative incidence curves are estimated by Aalen–Johansen method, truncated at Day 820.
CI, confidence interval; csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; HR, hazard ratio.

SUBGROUP ANALYSES FOR ISCHEMIC STROKE

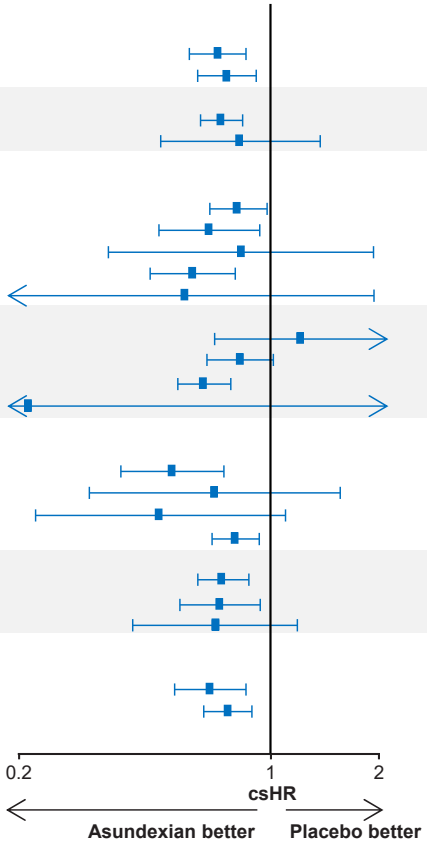
	Asundexian 50 mg n/N (%)	Placebo n/N (%)	csHR (95% CI)
Overall	**384/6162 (6.2%)**	**518/6165 (8.4%)**	0.74 (0.65–0.84)
Age			
<65 yr	128/2313 (5.5%)	176/2308 (7.6%)	0.73 (0.58–0.92)
65–75 yr	152/2318 (6.6%)	197/2318 (8.5%)	0.76 (0.61–0.94)
>75 yr	104/1531 (6.8%)	145/1539 (9.4%)	0.72 (0.56–0.92)
Sex			
Female	114/2063 (5.5%)	159/2047 (7.8%)	0.70 (0.55–0.89)
Male	270/4099 (6.6%)	359/4118 (8.7%)	0.75 (0.64–0.88)
Region			
North America	60/783 (7.7%)	86/782 (11.0%)	0.69 (0.50–0.96)
South America	14/281 (5.0%)	29/286 (10.1%)	0.48 (0.25–0.91)
Western Europe, Australia, and Israel	132/2425 (5.4%)	175/2419 (7.2%)	0.75 (0.60–0.94)
Eastern Europe	42/913 (4.6%)	68/910 (7.5%)	0.62 (0.42–0.91)
Asia-Pacific	136/1760 (7.7%)	160/1768 (9.0%)	0.86 (0.68–1.08)
Race			
White	235/4105 (5.7%)	314/4078 (7.7%)	0.74 (0.63–0.88)
Black	8/143 (5.6%)	25/139 (18.0%)	0.28 (0.13–0.62)
Asian	123/1721 (7.1%)	156/1742 (9.0%)	0.79 (0.63–1.01)
Other	18/193 (9.3%)	23/206 (11.2%)	0.86 (0.47–1.60)
Hypertension prior to randomization			
No	58/1225 (4.7%)	84/1297 (6.5%)	0.73 (0.52–1.02)
Yes	326/4937 (6.6%)	434/4868 (8.9%)	0.74 (0.64–0.85)
Diabetes prior to randomization			
No	214/4028 (5.3%)	281/4050 (6.9%)	0.77 (0.64–0.92)
Yes	170/2134 (8.0%)	237/2115 (11.2%)	0.70 (0.58–0.86)
History of stroke or TIA prior to index event			
No	238/4852 (4.9%)	325/4820 (6.7%)	0.73 (0.61–0.86)
Yes	146/1310 (11.1%)	193/1345 (14.3%)	0.77 (0.62–0.95)
Medical history of atherosclerosis			
No	224/4172 (5.4%)	300/4165 (7.2%)	0.74 (0.62–0.88)
Yes	160/1990 (8.0%)	218/2000 (10.9%)	0.74 (0.60–0.91)
Vascular imaging evidence of atherosclerosis			
No	23/528 (4.4%)	40/550 (7.3%)	0.58 (0.35–0.97)
Yes	361/5634 (6.4%)	478/5615 (8.5%)	0.75 (0.66–0.86)



CIs are unadjusted for multiplicity and may not be used for inference.
CI, confidence interval; csHR, cause-specific hazard ratio; TIA, transient ischemic attack.

SUBGROUP ANALYSES FOR ISCHEMIC STROKE

	Asundexian 50 mg n/N (%)	Placebo n/N (%)	csHR (95% CI)
Brain imaging demonstrating an acute non-lacunar infarct			
No	193/3173 (6.1%)	266/3158 (8.4%)	0.72 (0.60–0.86)
Yes	191/2989 (6.4%)	252/3007 (8.4%)	0.76 (0.63–0.92)
Type of index event			
Ischemic stroke	358/5839 (6.1%)	485/5838 (8.3%)	0.73 (0.64–0.84)
TIA	26/323 (8.0%)	33/325 (10.2%)	0.83 (0.49–1.38)
Stroke subtype (TOAST) classification*			
Large-artery atherosclerosis	203/2512 (8.1%)	247/2484 (9.9%)	0.82 (0.68–0.98)
Small-vessel occlusion (lacune)	59/1290 (4.6%)	90/1349 (6.7%)	0.68 (0.49–0.94)
Stroke of other determined etiology	9/161 (5.6%)	13/188 (6.9%)	0.84 (0.36–1.96)
Stroke of undetermined etiology	83/1786 (4.6%)	127/1710 (7.4%)	0.61 (0.46–0.81)
Cardioembolism	4/89 (4.5%)	8/107 (7.5%)	0.58 (0.17–1.95)
Time from index event to randomization			
≤24 hours	27/335 (8.1%)	24/356 (6.7%)	1.22 (0.70–2.11)
>24–48 hours	152/2190 (6.9%)	181/2150 (8.4%)	0.83 (0.67–1.03)
>48–72 hours	204/3592 (5.7%)	310/3630 (8.5%)	0.66 (0.55–0.78)
>72 hours	1/45 (2.2%)	3/29 (10.3%)	0.22 (0.02–2.08)
Intravenous thrombolysis and/or endovascular therapy for index stroke*			
Intravenous thrombolysis only	54/1146 (4.7%)	99/1168 (8.5%)	0.54 (0.39–0.75)
Endovascular therapy only	11/202 (5.4%)	13/169 (7.7%)	0.71 (0.32–1.57)
Intravenous thrombolysis and endovascular therapy	9/260 (3.5%)	18/256 (7.0%)	0.50 (0.22–1.11)
Neither intravenous thrombolysis nor endovascular therapy	284/4231 (6.7%)	355/4245 (8.4%)	0.80 (0.69–0.94)
NIHSS score of index stroke at randomization*			
≤3	240/4087 (5.9%)	321/4079 (7.9%)	0.74 (0.63–0.87)
4–7	95/1385 (6.9%)	130/1375 (9.5%)	0.73 (0.56–0.95)
≥8	23/365 (6.3%)	33/382 (8.6%)	0.71 (0.41–1.20)
Planned dual antiplatelet therapy with aspirin and a P2Y12 inhibitor			
No	119/2303 (5.2%)	174/2312 (7.5%)	0.68 (0.54–0.86)
Yes	265/3859 (6.9%)	344/3853 (8.9%)	0.77 (0.65–0.90)



*For index event of ischemic stroke.
CIs are unadjusted for multiplicity and may not be used for inference.
CI, confidence interval; csHR, cause-specific hazard ratio; NIHSS, National Institutes of Health Stroke Scale; P2Y12, purinergic receptor Y12; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

CONCLUSION

- In patients with non-cardioembolic ischemic stroke or high-risk TIA treated with antiplatelet therapy, asundexian 50 mg reduced the occurrence of ischemic stroke (csHR 0.74; 95% CI, 0.65 to 0.84; p<0.001)
  - The difference between the treatment arms began early and continued throughout the treatment period.
  - A consistent effect was seen in subgroups.

- Asundexian was associated with a reduction in disabling or fatal stroke (mRS ≥ 3)

- Asundexian was not associated with an increase in bleeding
  - Including ISTH major,
  - CRNM, minor or intracranial bleeding

CI, confidence interval; csHR, cause-specific hazard ratio; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; mRS, modified Rankin score; TIA, transient ischemic attack.

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- We thank the Steering Committee and independent Data Monitoring Committee members, the study operations teams, the investigators, the study site coordinators, and especially the patients and their families, who made this study possible

Steering Committee

Mike Sharma (Chair), Ashkan Shoamanesh (Co-Chair), Pierre Amarenco, Pablo Amaya, Sebastian Francisco Ameriso, Hee-Joon Bae, Daniel Bereczki, Bruce Campbell, Hanne Christensen, Charlotte Cordonnier, Jonathan Coutinho, Gian Marco De Marchis, Andrew Demchuk, Qiang Dong, John Eikelboom, Jose Ferro, Teruyuki Hirano, Fan Kee Hoo, Scott Kasner, Michael Knoflach, Martin Kovar, I-Hui Lee, Ronen Leker, Robin Lemmens, Arne Lindgren, Jaime Masjuan, Vaidas Matijosaitis, Evija Miglane, Robert Mikulik, Eva Muehlhofer, Hardi Mundl, Serefnur Ozturk, Jukka Putaala, Tom Robinson, Gisele Sampaio Silva, Else Sandset, Jeff Saver, Kevin Sheth, Agnieszka Slowik, Ivan Staikov, PN Sylaja, Cristina Tiu, Georgios Tsivgoulis, Peter Turcani, Saule Turuspekova, H. Bart van der Worp, Roland Veltkamp, Andrea Zini

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THANK YOU

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