Inibizione del fattore XIa con asundexian dopo ictus ischemico non cardioembolico

Risultati del trial PACIFIC-Stroke

Background

- Non-cardioembolic ischaemic strokes account for 75% of all ischaemic strokes.
- The recurrence rate is more than 6% in the year after stroke despite guideline-recommended treatment.
- There is a substantial burden of covert brain infarction during the year after stroke, which have been associated with cognitive and functional decline.
- Guideline-recommended antithrombotic prophylaxis of patients who have non-cardioembolic ischaemic stroke includes long-term single antiplatelet therapy, sometimes after short-term dual antiplatelet therapy.

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Background

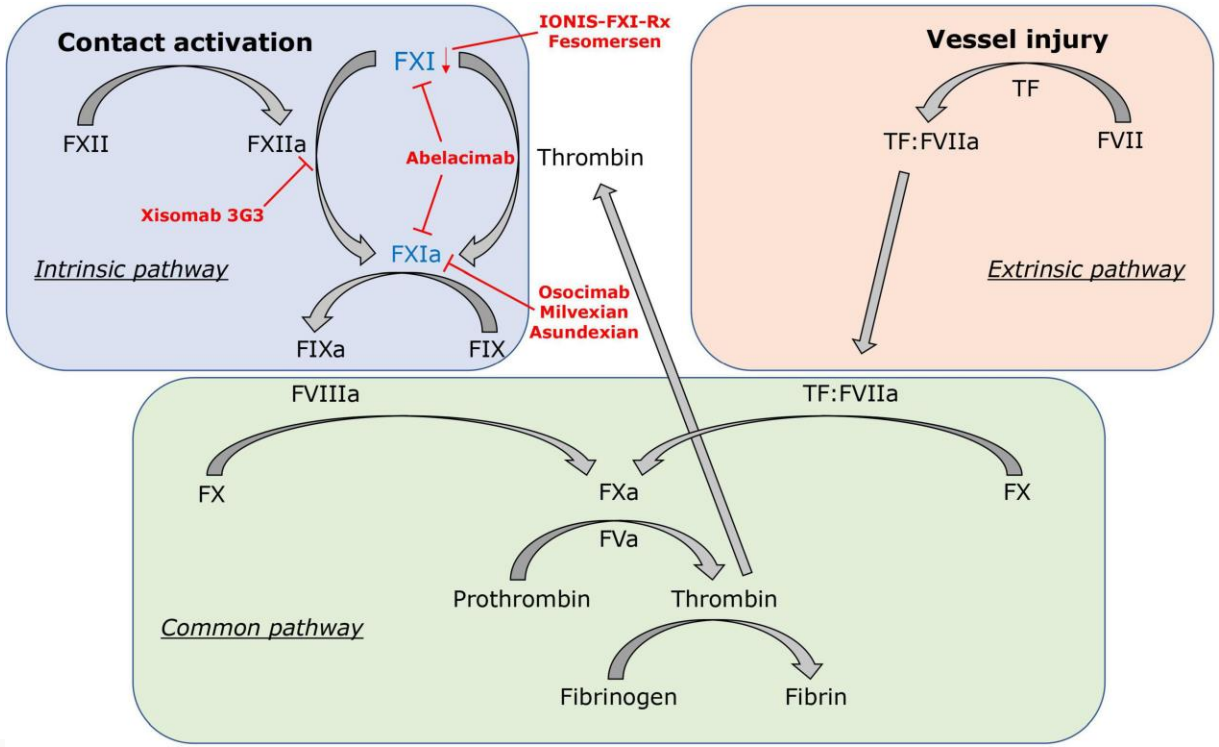
- No clinical studies have established a benefit of anticoagulation for secondary prevention in patients with non-cardioembolic ischaemic stroke
- Dual pathway antithrombotic therapy substantially reduced ischaemic stroke recurrence compared with aspirin alone in patients with stable coronary and peripheral artery atherosclerosis in the COMPASS trial.

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001	0.90 (0.79–1.03)	0.12
Secondary outcomes‡							
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001	0.88 (0.77–1.01)	0.06
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001	0.88 (0.77–0.99)	0.04
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71–0.96)	0.01	0.97 (0.84–1.12)	0.67
Other outcomes§							
CV death	160 (1.7)	195 (2.1)	203 (2.2)	0.78 (0.64–0.96)	0.02	0.96 (0.79–1.17)	0.69
Non-CV death	153 (1.7)	171 (1.9)	175 (1.9)	0.87 (0.70–1.08)	0.20	0.98 (0.79–1.21)	0.84
Death from CHD	86 (0.9)	128 (1.4)	117 (1.3)	0.73 (0.55–0.96)	0.03	1.09 (0.85–1.41)	0.48
Stroke¶	83 (0.9)	117 (1.3)	142 (1.6)	0.58 (0.44–0.76)	<0.001	0.82 (0.65–1.05)	0.12
Ischemic or uncertain type	68 (0.7)	91 (1.0)	132 (1.4)	0.51 (0.38–0.68)	<0.001	0.69 (0.53–0.90)	0.006
Hemorrhagic	15 (0.2)	27 (0.3)	10 (0.1)	1.49 (0.67–3.31)	0.33	2.70 (1.31–5.58)	0.005
Myocardial infarction	178 (1.9)	182 (2.0)	205 (2.2)	0.86 (0.70–1.05)	0.14	0.89 (0.73–1.08)	0.24
Heart failure	197 (2.2)	191 (2.1)	192 (2.1)	1.02 (0.84–1.24)	0.84	0.99 (0.81–1.21)	0.95
Venous thromboembolism	25 (0.3)	36 (0.4)	41 (0.4)	0.61 (0.37–1.00)	0.05	0.88 (0.56–1.38)	0.58
Hospitalization							
For CV causes	1303 (14.2)	1317 (14.4)	1394 (15.3)	0.92 (0.86–1.00)	0.04	0.94 (0.87–1.01)	0.11
For non-CV causes	1701 (18.6)	1649 (18.1)	1624 (17.8)	1.05 (0.98–1.13)	0.14	1.02 (0.95–1.09)	0.54

N Engl J Med 2017; 377:1319-1330

Asundexian

- Asundexian is an oral direct inhibitor of activated coagulation factor XI (FXIa) that might have less associated bleeding than other available anticoagulants.

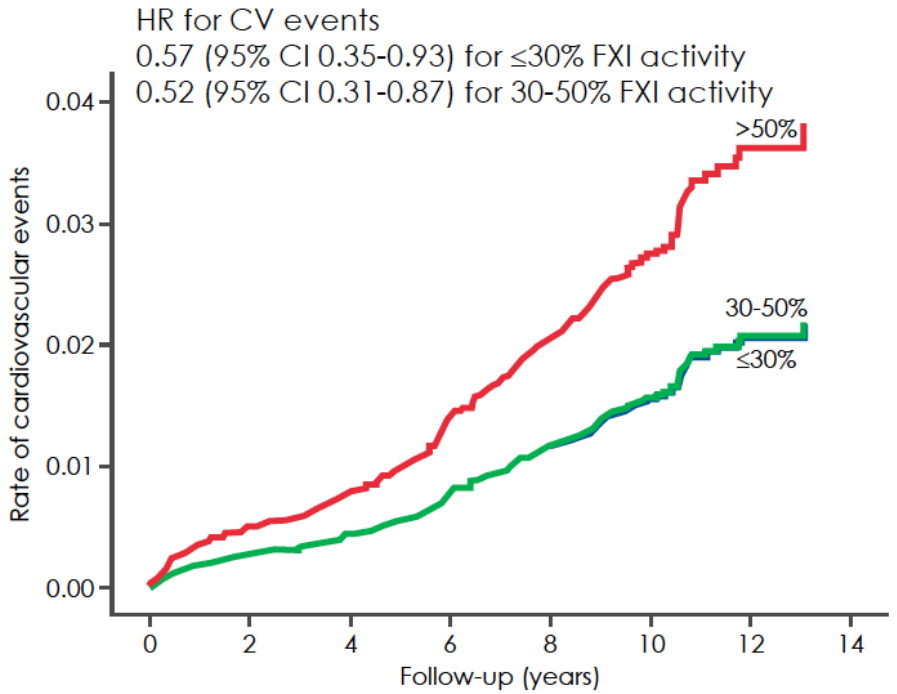


Front cardiovasc Med. 2022 May 12;9:903029

Asundexian

- Patients with ischaemic stroke have increased levels of FXI, and patients with inherited FXI deficiency have lower risks of stroke.
- Phase 2 randomised trials have found effective prevention of thromboembolism and low risk of bleeding associated with use of FXI and FXIa inhibitors in patients undergoing total knee arthroplasty.
- Asundexian is an attractive candidate for assessment as a potential add-on to antiplatelet therapy in patients with acute ischaemic stroke for secondary stroke prevention.

Significant reduced risk for CV events and ischemic stroke in FXI-deficient individuals



Preis M, at al. (Blood. 2017;129(9):1210-121

Odds ratio for ischemic stroke 0.47 (95% CI 0.36-0.61)

Georgi B, et al. (Stroke. 2019;50:3004-3012

Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial

Ashkan Shoamanesh, Hardi Mundl, Eric E Smith, Jaime Masjuan, Ivan Milanov, Teruyuki Hirano, Alina Agafina, Bruce Campbell, Valeria Caso, Jean-Louis Mas, Qiang Dong, Peter Turcani, Hanne Christensen, Jose M Ferro, Roland Veltkamp, Robert Mikulik, Gian Marco De Marchis, Thompson Robinson, Robin Lemmens, Adam Stepien, Stefan Greisenegger, Risto Roine, Laszlo Csiba, Pooja Khatri, Jonathan Coutinho, Arne G Lindgren, Andrew M Demchuk, Pablo Colorado, Bodo Kirsch, Christoph Neumann, Laura Heenan, Lizhen Xu, Stuart J Connolly, Robert G Hart, for the PACIFIC-Stroke Investigators

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Methods

- Randomised, double-blind, placebo-controlled, phase 2b dose-finding trial
- Patients with acute (within 48 h) non-cardioembolic ischaemic stroke were recruited from 196 hospitals in 23 countries.
- Patients eligible if:
  - >45 years or older,
  - treated with antiplatelet therapy,
  - able to have a baseline MRI (either before or within 72 h of randomisation).
- Randomly assigned (1:1:1:1), using an interactive web-based response system and stratified according to anticipated antiplatelet therapy (single vs dual), to once daily oral asundexian 10 mg, 20 mg, or 50 mg, or placebo in addition to usual antiplatelet therapy
- Followed up during treatment for 26–52 weeks.
- Brain MRIs were obtained at study entry and at 26 weeks or as soon as possible after treatment discontinuation.

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Enpoints

- The primary efficacy outcome was the dose–response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischaemic stroke at or before 26 weeks after randomisation.
- The primary safety outcome was major or clinically relevant non-major bleeding as defined by International Society on Thrombosis and Haemostasis criteria.
- The efficacy outcome was assessed in all participants assigned to treatment, and the safety outcome was assessed in all participants who received at least one dose of study treatment.

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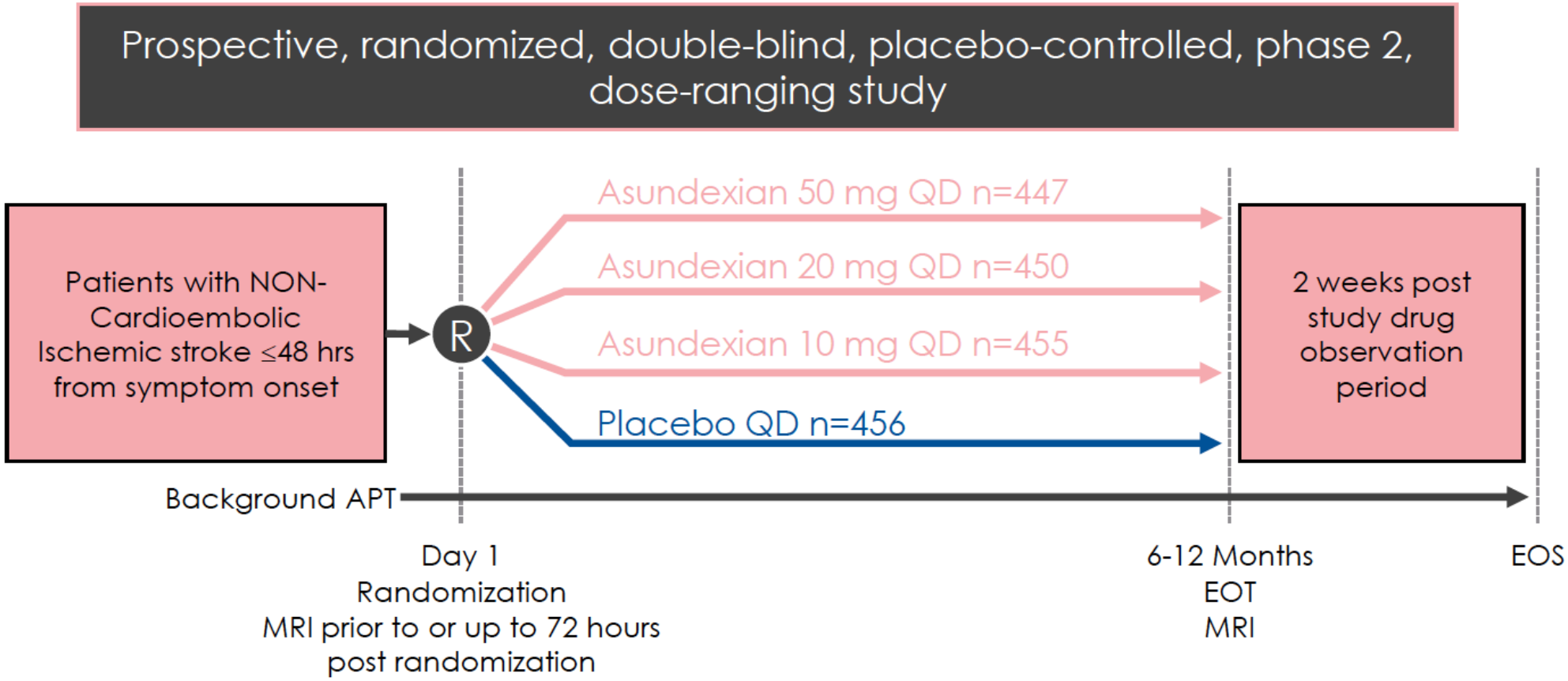
Trial profile



Enrollment: 1808 patients between June 15, 2020 and July 22, 2021 at 196 sites in 23 countries

Baseline characteristics

	Total (n=1808)	Placebo group (n=456)	Asundexian 10 mg group (n=455)	Asundexian 20 mg group (n=450)	Asundexian 50 mg group (n=447)
Age, years	67·0 (9·9)	66·6 (10·1)	66·8 (10·1)	67·6 (9·4)	67·0 (10·0)
Sex					
Female	615 (34%)	150 (33%)	161 (35%)	150 (33%)	154 (34%)
Male	1193 (66%)	306 (67%)	294 (65%)	300 (67%)	293 (66%)
Self-reported race					
White	1505 (83%)	380 (83%)	381 (84%)	377 (84%)	367 (82%)
Black	18 (1%)	3 (1%)	4 (1%)	3 (1%)	8 (2%)
Asian	268 (15%)	66 (14%)	67 (15%)	67 (15%)	68 (15%)
Other	3 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Geographical region					
North America	23 (1%)	6 (1%)	6 (1%)	6 (1%)	5 (1%)
Western Europe and Australia	1007 (56%)	255 (56%)	253 (56%)	251 (56%)	248 (55%)
Eastern Europe	524 (29%)	131 (29%)	132 (29%)	130 (29%)	131 (29%)
Asia	254 (14%)	64 (14%)	64 (14%)	63 (14%)	63 (14%)
Bodyweight, kg	78·9 (16·6)	79·2 (16·0)	78·5 (17·4)	78·6 (16·4)	79·2(16·5)
BMI, kg/m²	27·5 (4·8)	27·4 (4·7)	27·4 (5·0)	27·4 (4·8)	27·6 (4·9)
Current tobacco use	484 (27%)	126 (28%)	123 (27%)	113 (25%)	122 (27%)
Previous medical conditions					
Hypertension	1392 (77%)	346 (76%)	366 (80%)	333 (74%)	347 (78%)
Diabetes	501 (28%)	127 (28%)	122 (27%)	137 (30%)	115 (26%)
Hyperlipidaemia	955 (53%)	246 (54%)	225 (49%)	228 (51%)	256 (57%)
Heart failure	104 (6%)	24 (5%)	28 (6%)	26 (6%)	26 (6%)
Coronary artery disease	167 (9%)	37 (8%)	43 (9%)	41 (9%)	46 (10%)
Myocardial infarction	81 (4%)	17 (4%)	23 (5%)	18 (4%)	23 (5%)
Percutaneous coronary intervention or angioplasty, or coronary artery bypass grafting	80 (4%)	19 (4%)	16 (4%)	23 (5%)	22 (5%)
Carotid endarterectomy or stenting	13 (1%)	2 (<1%)	3 (1%)	4 (1%)	4 (1%)
Peripheral artery disease	45 (2%)	13 (3%)	11 (2%)	9 (2%)	12 (3%)
Chronic kidney disease	93 (5%)	29 (6%)	19 (4%)	29 (6%)	16 (4%)
Previous stroke or transient ischaemic attack	285 (16%)	75 (16%)	77 (17%)	68 (15%)	65 (15%)
History of gastrointestinal bleeding	18 (1%)	7 (2%)	3 (1%)	2 (<1%)	6 (1%)

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Baseline characteristics

	Total (n=1808)	Placebo group (n=456)	Asundexian 10 mg group (n=455)	Asundexian 20 mg group (n=450)	Asundexian 50 mg group (n=447)
Qualifying stroke subtype*					
Large-artery atherosclerosis	320 (18%)	76 (17%)	82 (18%)	73 (16%)	89 (20%)
Small-vessel occlusion	817 (45%)	210 (46%)	205 (45%)	196 (44%)	206 (46%)
Stroke of other determined aetiology	45 (2%)	6 (1%)	15 (3%)	10 (2%)	14 (3%)
Stroke of undetermined aetiology	616 (34%)	162 (36%)	149 (33%)	168 (37%)	137 (31%)
Cardioembolism	9 (<1%)	2 (<1%)	3 (1%)	3 (1%)	1 (<1%)
Extracranial or intracranial atherosclerosis proximal to the qualifying stroke	607 (34%)	142 (31%)	150 (33%)	161 (36%)	154 (34%)
Carotid artery atherosclerosis identified by vascular imaging	650 (36%)	166 (36%)	162 (36%)	170 (38%)	152 (34%)
NIHSS score at randomisation†					
Mean (SD)	2·8 (2·2)	2·9 (2·2)	2·8 (2·3)	2·7 (2·1)	3·0 (2·3)
8–15	58 (3%)	17 (4%)	14 (3%)	11 (2%)	16 (4%)
Day 7 mRS score‡	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)	1·0 (1·0–2·0)
Dual antiplatelet therapy before index event	39 (2%)	8 (2%)	13 (3%)	10 (2%)	8 (2%)
Dual antiplatelet therapy after index event	783 (43%)	199 (44%)	197 (43%)	195 (43%)	192 (43%)
Blood pressure at randomisation, mm Hg					
Systolic blood pressure	138 (14)	137 (14)	139 (14)	138 (14)	139 (14)
Diastolic blood pressure	79 (10)	79 (10)	79 (11)	79 (10)	79 (10)
eGFR, mL/min per 1·73 m²§	79 (21)	79 (22)	79 (21)	79 (20)	78 (20)
Time from qualifying stroke to randomisation, h					
Median (IQR)	38 (30–44)	37 (29–44)	40 (30–45)	38 (30–44)	38 (29–45)
≤24 h	193 (11%)	49 (11%)	41 (9%)	52 (12%)	51 (11%)
Thrombolysis before randomisation	217 (12%)	59 (13%)	59 (13%)	48 (11%)	51 (11%)
Endovascular thrombectomy before randomisation	52 (3%)	11 (2%)	15 (3%)	12 (3%)	14 (3%)

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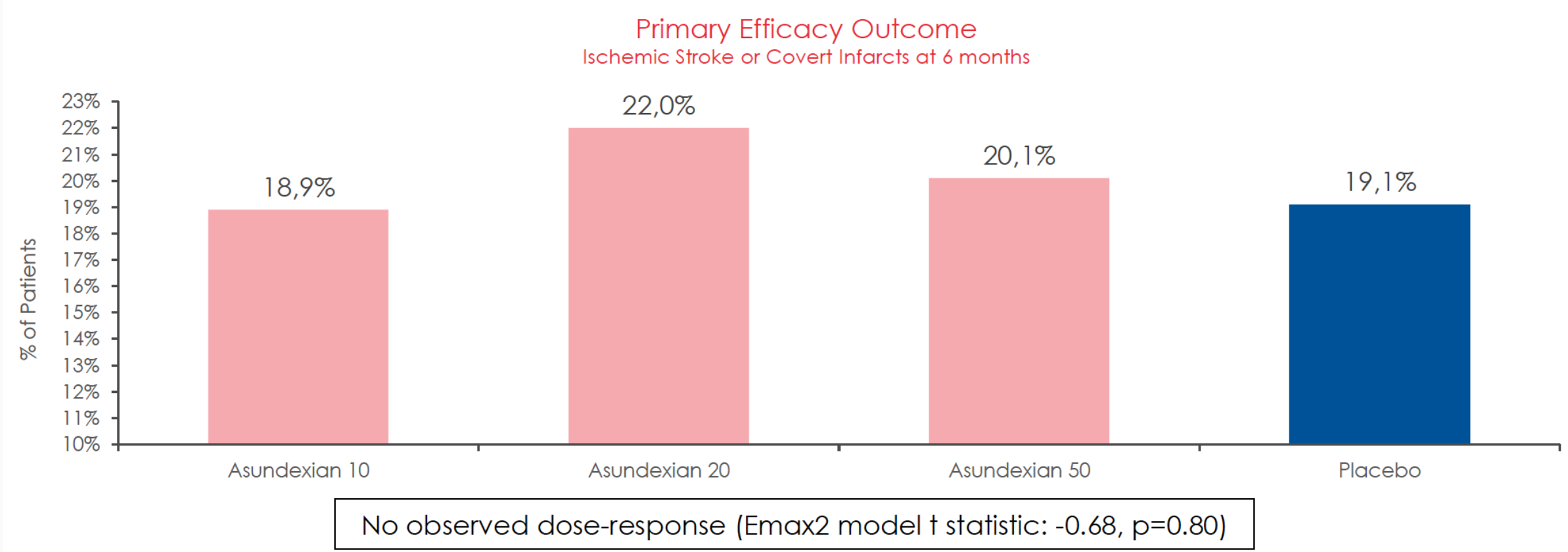
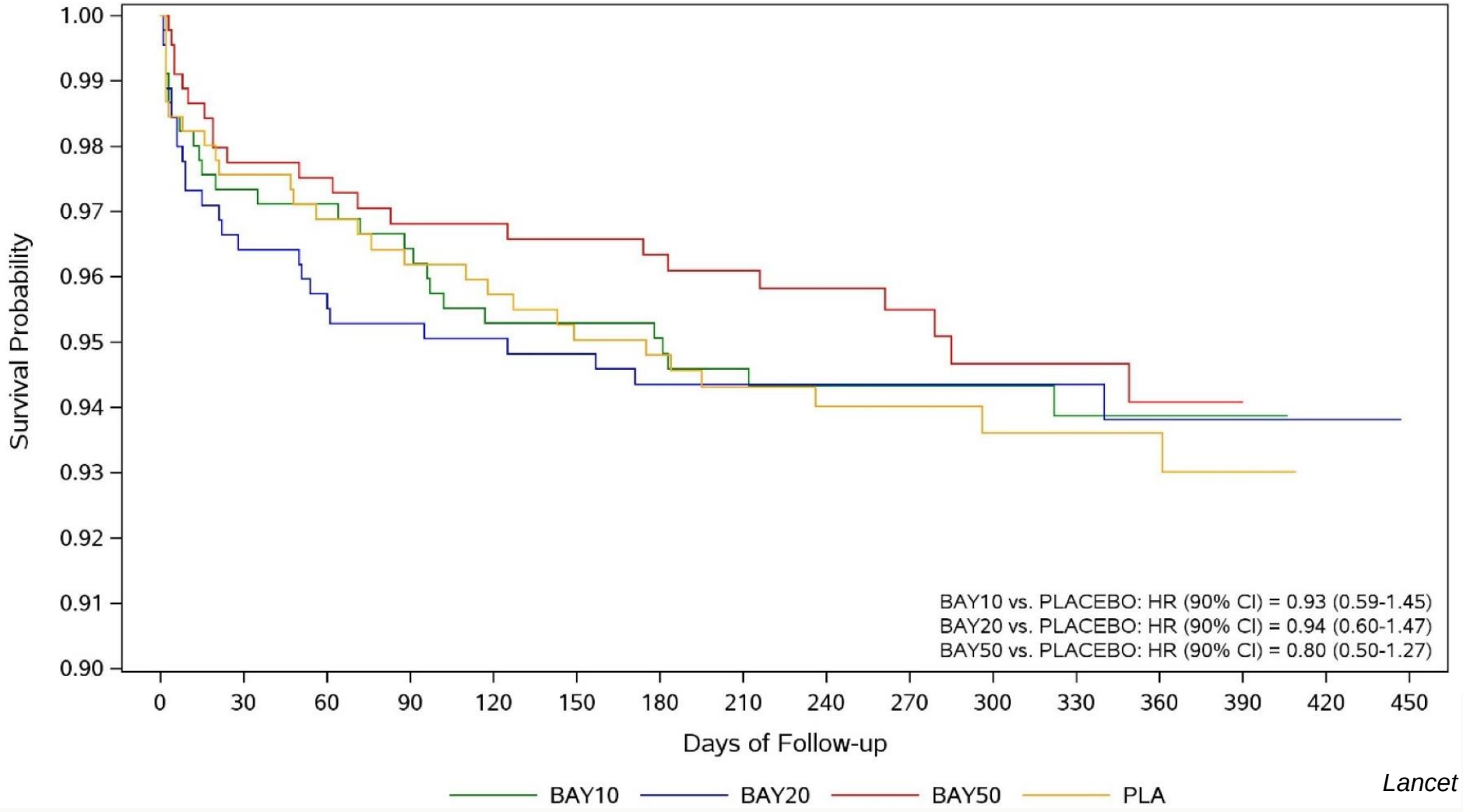
Efficacy outcome

	Placebo (n=456)	Asundexian 10 mg group (n=455)	Asundexian 10 mg *vs* placebo	Asundexian 20 mg group (n=450)	Asundexian 20 mg *vs* placebo	Asundexian 50 mg group (n=447)	Asundexian 50 mg *vs* placebo
Primary outcome							
Ischaemic stroke or covert infarcts*	87 (19%)	86 (19%)	0·99 (0·79–1·24)	99 (22%)	1·15 (0·93–1·43)	90 (20%)	1·06 (0·85–1·32)
Secondary outcomes							
Components of the primary outcome*							
Incident covert brain infarcts on MRI†	64 (14%)	63 (14%)	0·99 (0·75–1·30)	74 (16%)	1·17 (0·90–1·51)	74 (17%)	1·17 (0·91–1·52)
Recurrent symptomatic ischaemic stroke*	23 (5%)	24 (5%)	1·05 (0·66–1·67)	25 (6%)	1·10 (0·69–1·75)	17 (4%)	0·75 (0·45–1·26)
Efficacy outcomes‡							
Recurrent symptomatic ischaemic stroke§	28 (6%)	26 (6%)	0·93 (0·59–1·45)	26 (6%)	0·94 (0·60–1·47)	22 (5%)	0·80 (0·50–1·27)
Any recurrent stroke§	30 (7%)	26 (6%)	0·86 (0·56–1·34)	26 (6%)	0·88 (0·56–1·36)	25 (6%)	0·85 (0·54–1·32)
Disabling stroke (mRS score of ≥4)§	3 (1%)	5 (1%)	1·67 (0·50–5·55)	5 (1%)	1·69 (0·51–5·62)	1 (<1%)	0·34 (0·05–2·27)
Recurrent symptomatic ischaemic stroke, vascular death, or myocardial infarction§	35 (8%)	33 (7%)	0·94 (0·63–1·40)	30 (7%)	0·87 (0·58–1·30)	33 (7%)	0·96 (0·64–1·43)
Recurrent symptomatic ischaemic stroke, incident covert brain infarct on MRI, cardiovascular death, myocardial infarction and systemic embolism*	79 (17%)	80 (18%)	0·95 (0·76–1·20)	87 (19%)	1·06 (0·85–1·33)	81 (18%)	1·03 (0·82–1·30)
All-cause mortality§	10 (2%)	10 (2%)	1·00 (0·48–2·09)	6 (1%)	0·60 (0·26–1·41)	17 (4%)	1·72 (0·89–3·32)
Post-hoc exploratory outcomes‡							
Transient ischaemic attack	11 (2%)	10 (2%)	0·91 (0·44–1·87)	2 (<1%)	0·18 (0·05–0·64)	2 (<1%)	0·18 (0·05–0·65)
Recurrent symptomatic ischaemic stroke or transient ischaemic attack	38 (8%)	35 (8%)	0·92 (0·63–1·35)	28 (6%)	0·74 (0·49–1·12)	24 (5%)	0·64 (0·41–0·98)

Primary efficacy outcome



Kaplan-Meier curves for recurrent symptomatic ischaemic stroke (intention-to-treat)



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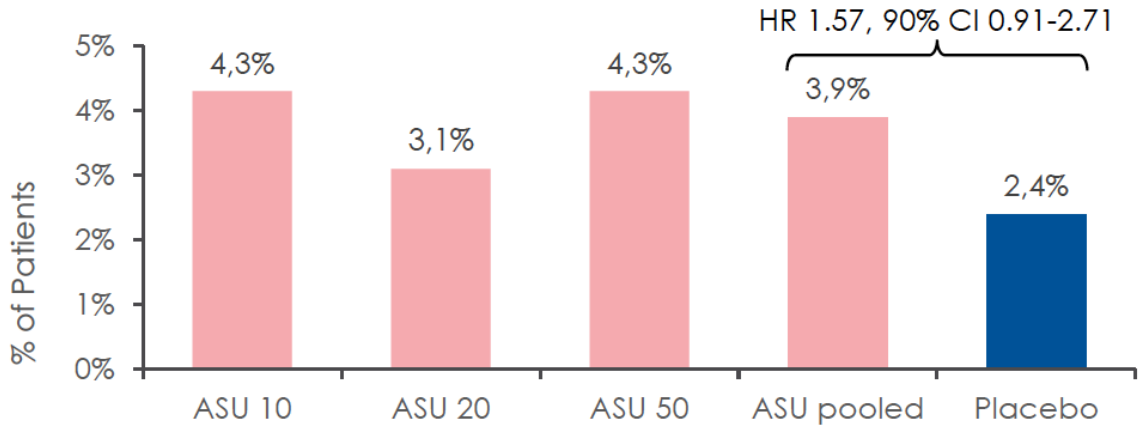
Safety outcome

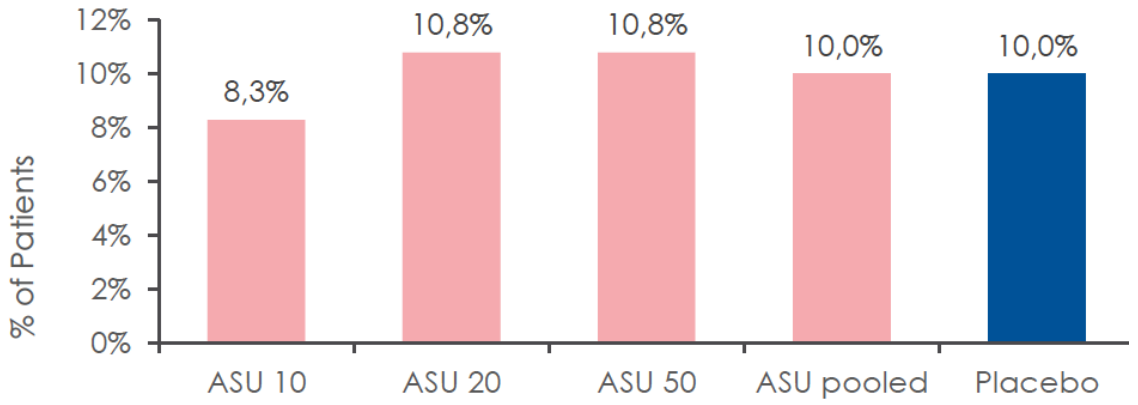
	Placebo group (n=452)	Asundexian 10 mg group (n=445)	Asundexian 10 mg *vs* placebo	Asundexian 20 mg group (n=446)	Asundexian 20 mg *vs* placebo	Asundexian 50 mg group (n=443)	Asundexian 50 mg *vs* placebo	Asundexian all doses (n=1334)	Asundexian all doses *vs* placebo
Primary safety outcome*									
ISTH-defined major and clinically relevant non-major bleeding	11 (2%)	19 (4%)	1·71 (0·91–3·18)	14 (3%)	1·27 (0·66–2·47)	19 (4%)	1·74 (0·93–3·24)	52 (4%)	1·57 (0·91–2·71)
Secondary safety outcomes*									
All bleeding	44 (10%)	37 (8%)	0·82 (0·57–1·18)	48 (11%)	1·11 (0·79–1·56)	48 (11%)	1·10 (0·78–1·54)	133 (10%)	1·01 (0·76–1·34)
ISTH-defined major bleeding	4 (1%)	4 (1%)	0·98 (0·31–3·15)	3 (1%)	0·76 (0·22–2·66)	7 (2%)	1·76 (0·63–4·94)	14 (1%)	1·17 (0·46–2·96)
ISTH-defined clinically relevant non-major bleeding	7 (2%)	15 (3%)	2·11 (0·99–4·48)	12 (3%)	1·71 (0·78–3·75)	12 (3%)	1·72 (0·79–3·76)	39 (3%)	1·85 (0·94–3·64)
ISTH-defined minor bleeding	34 (8%)	21 (5%)	0·60 (0·38–0·95)	39 (9%)	1·17 (0·79–1·72)	34 (8%)	1·01 (0·67–1·50)	94 (7%)	0·92 (0·66–1·28)
Intracerebral haemorrhage	1 (<1%)	0	..	0	..	3 (1%)	3·05 (0·46–20·4)	3 (<1%)	1·00 (0·15–6·70)
Exploratory safety outcomes†									
Haemorrhagic infarction 1 and 2 on baseline MRI done after first dose of study drug (up to 72 h after randomisation)‡	93/296 (31%)	82/277 (30%)	0·94 (0·77–1·16)	78/265 (29%)	0·94 (0·76–1·16)	84/277 (30%)	0·97 (0·79–1·19)	244/819 (30%)	0·95 (0·80–1·12)
Parenchymal haematoma 1 and 2 on baseline MRI done after first dose of study drug (up to 72 h after randomisation)‡	4/296 (1%)	3/277 (1%)	0·80 (0·23–2·79)	1/265 (<1%)	0·28 (0·04–1·75)	0/277	..	4/819 (<1%)	0·36 (0·11–1·15)
New haemorrhagic infarction 1 and 2 on follow-up MRI§	47/323 (15%)	50/319 (16%)	1·08 (0·79–1·47)	53/332 (16%)	1·10 (0·81–1·49)	56/320 (18%)	1·20 (0·89–1·62)	159/971 (16%)	1·13 (0·87–1·45)
New parenchymal haematoma 1 and 2 on follow-up MRI§	1/323 (<1%)	0/319	..	1/332 (<1%)	0·97 (0·10–9·93)	0/320	..	1/971 (<1%)	0·33 (0·03–3·40)

Safety outcome

A. Major or clinically-Relevant Non-Major Bleeding (ISTH)



B. All Bleeding

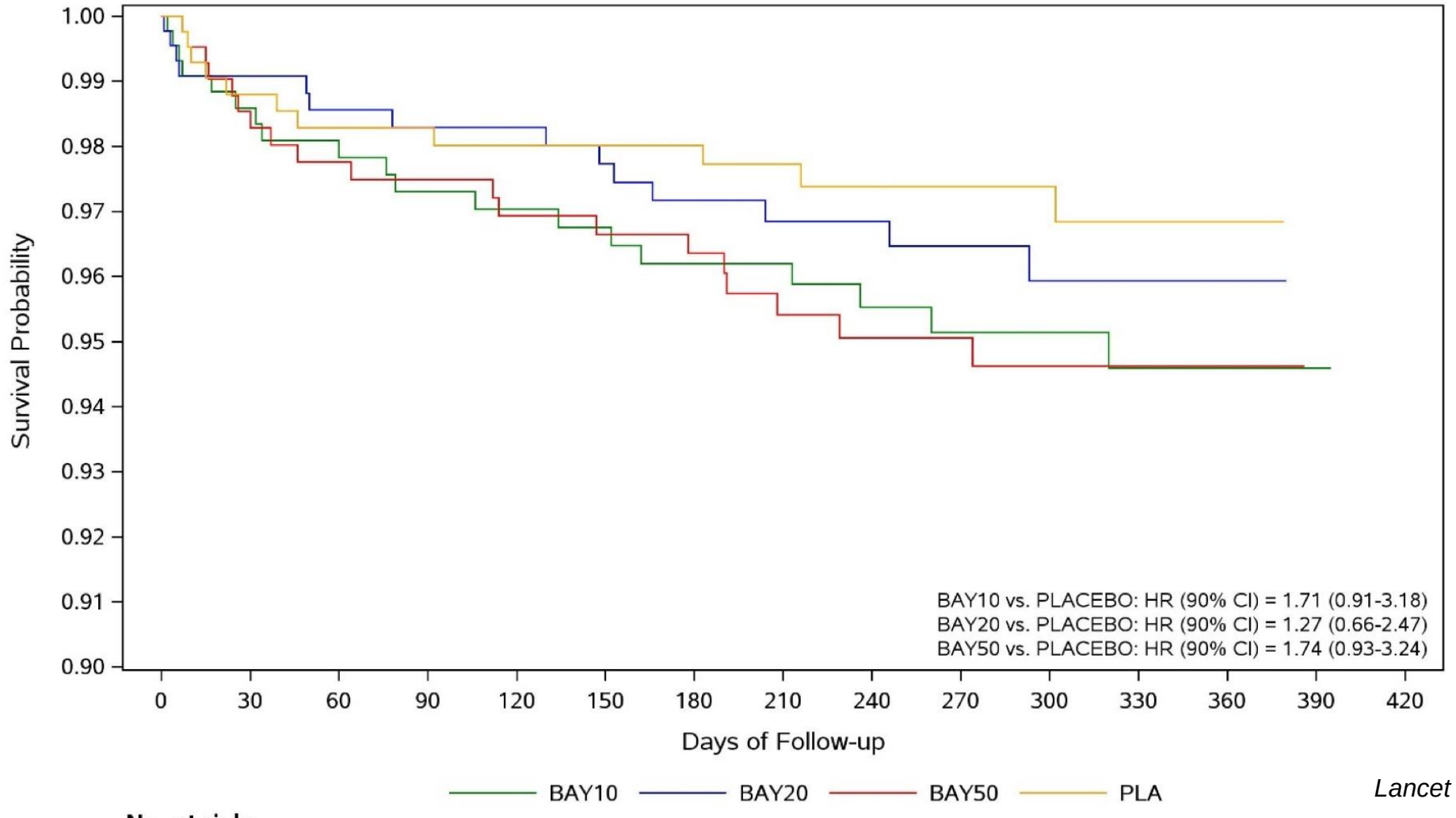


C. Hemorrhagic transformation in patients with baseline MRI after randomization

	Asundexian, 10 (N=455)	Asundexian, 20 (N=450)	Asundexian, 50 (N=447)	Placebo (N=456)
HI1 and 2	29.6%	29.4%	30.3%	32.8%
PH1 and 2	1.1%	0.4%	0%	1.4%

No significant increase in bleeding and hemorrhagic transformation of index stroke

Kaplan-Meier curves for ISTH major and clinically - relevant non-major bleeding (on-treatment)



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Limitations

- The PACIFIC-Stroke phase 2 study was intended to inform the design of a subsequent phase 3 randomised trial, and as such has limitations related to statistical power for secondary outcomes and subgroup analyses.
- A substantial proportion of participants did not undergo serial study MRIs, requiring imputation of results for the outcome of incident covert brain infarction.
- Haemorrhagic transformation is more frequent with large infarcts, and despite eligibility allowing patients with NIHSS scores up to 15 to participate during part B, the cohort's mean NIHSS score at the time of randomisation was relatively low (mean 2.8), restricting the generalisability of our findings to patients with mild strokes.
- The post-hoc and exploratory nature of several of our notable findings should be interpreted with caution and require validation through future research.

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Conclusions

- In patients with acute non-cardioembolic ischaemic stroke of mild-to-moderate severity treated with antiplatelet therapy, asundexian did not reduce the composite primary outcome of symptomatic recurrent ischaemic stroke and incident covert brain infarcts on MRI in a dose-dependent manner.
- However, in post-hoc and exploratory analyses, asundexian 50 mg daily provided superior protection against the composite of recurrent ischaemic stroke and transient ischaemic attack relative to placebo, especially in patients with atherosclerosis, without increasing the risk of major or clinically relevant non-major bleeding. These promising results require confirmation by an adequately powered phase 3 randomised trial.

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Summary

Evidence before this study

Antiplatelet therapy is the guideline-recommended antithrombotic prophylaxis for secondary prevention of non-cardioembolic ischaemic stroke. The benefit of anticoagulation therapy in this setting has not been established. Dual pathway inhibition combining an anticoagulant with an antiplatelet agent is hypothetically appealing, but this approach has not been explored to date due to the absence of safe oral anticoagulants. Factor XIa (FXIa) inhibitors, such as asundexian, might prevent thrombosis without increasing bleeding.

Added value of this study

This is the first randomised placebo-controlled trial to assess the effect of FXIa inhibition, using asundexian, when added to antiplatelet therapy for secondary prevention of non-cardioembolic ischaemic stroke. No difference was seen between asundexian (10 mg, 20 mg, and 50 mg daily) versus placebo on the primary efficacy outcome of composite symptomatic recurrent ischaemic stroke and incident covert brain infarcts. And no difference was seen between asundexian and placebo for the primary safety endpoint of the composite of major bleeding and clinically relevant non-major bleeding, according to the criteria of the International Society on Thrombosis and Haemostasis. However, by post-hoc analysis, inhibition of FXIa with asundexian reduced the composite of recurrent ischaemic stroke and transient ischaemic attack compared with placebo in patients with acute, non-cardioembolic ischaemic stroke, particularly for those with atherosclerosis, without increasing bleeding.

Implications of all the available evidence

Although we found no difference between asundexian and placebo for the primary efficacy or safety endpoints, the post-hoc results from this phase 2 trial are promising and require independent validation in an adequately powered phase 3 randomised trial before being applied to clinical care for secondary stroke prevention.

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