Phase 2 Program of AntiCoagulation via Inhibition of FXIa by the Oral Compound BAY 2433334 – Non-Cardioembolic Stroke Study

Main Results of the PACIFIC-Stroke Study

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on behalf of the PACIFIC-Stroke Steering Committee and Investigators

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Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Disclosures

PACIFIC-Stroke: Bayer AG

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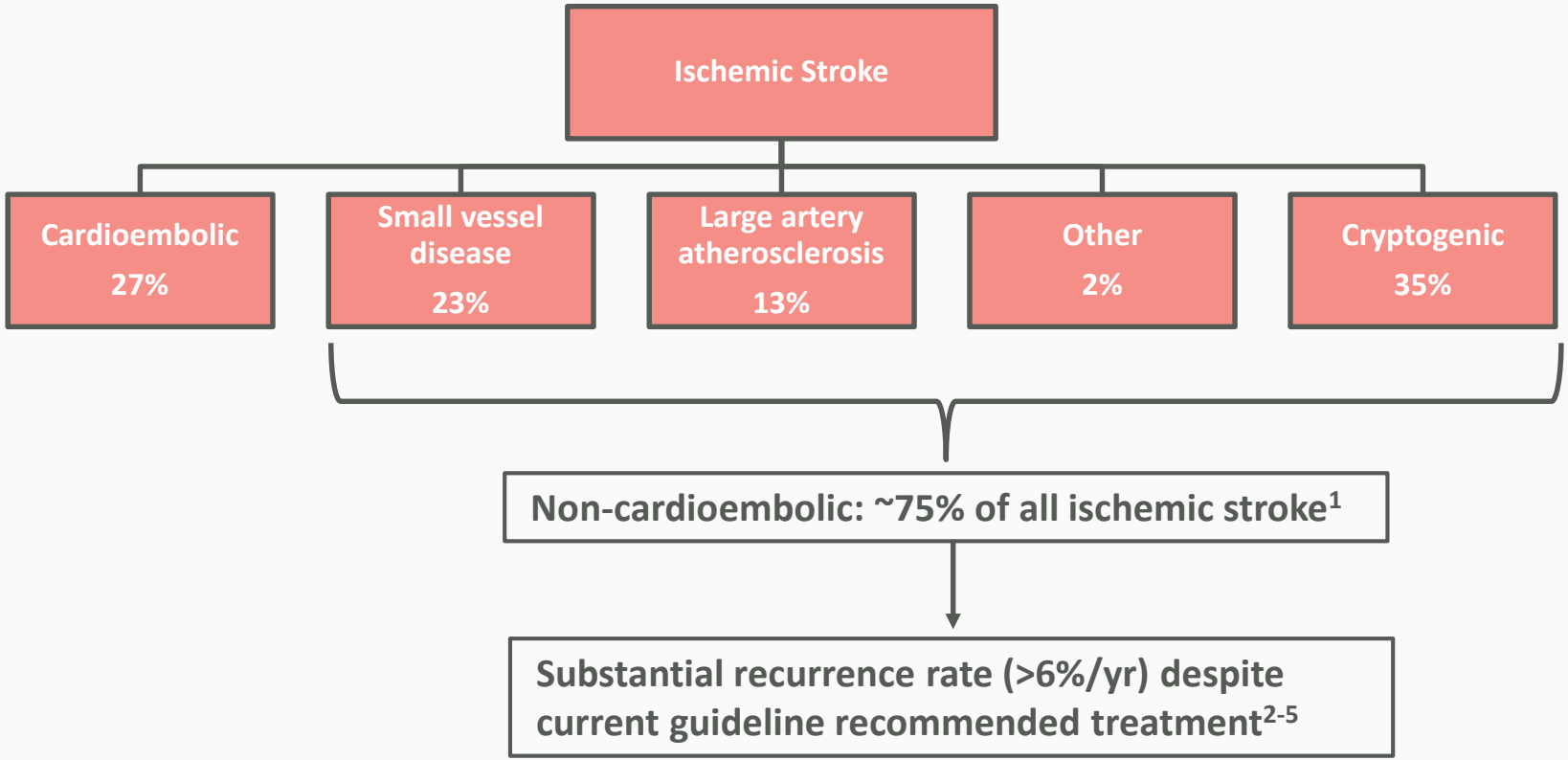
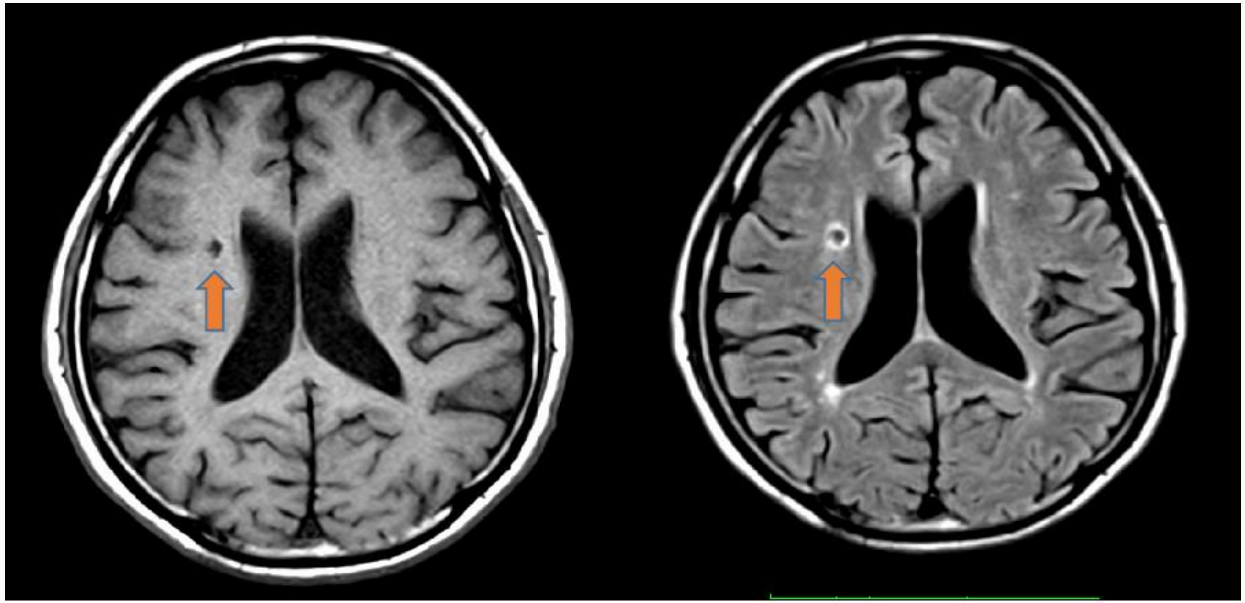
Non-Cardioembolic Ischemic Stroke



[1]Kleindorfer, et al. Stroke 2021; 52: e364–467; [2]Wang, et al. NEJM 2013; 369:11-9; [3]Johnston, et al. NEJM 2018; 379:215-25; [4]Johnston, et al. NEJM 2020;383:207-17; [5]Dawson, et al. Eur Stroke J 2022

Covert brain infarction

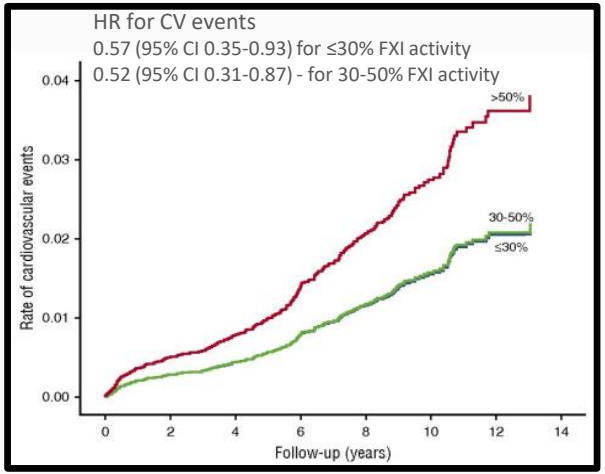


- **Substantial burden of covert brain infarction**
- **Contributor to post-stroke cognitive and functional decline[1,2]**

[1]Vermeer SE, et al. NEJM 2003;348:1215-22; [2]Durrani R, et al. Can J Neurol Sci 2020;47:456-63

Human genetic data as well as clinical data support the testing of asundexian, a FXIa inhibitor, for secondary stroke prevention

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

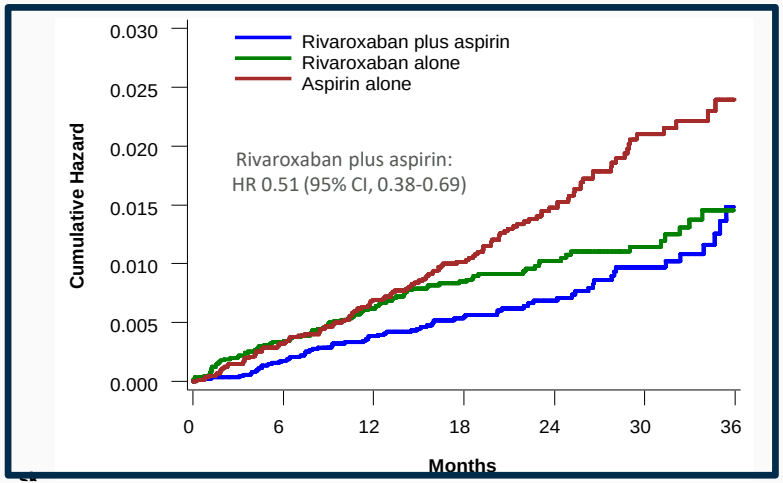


Preis M, et al. (Blood. 2017;129(9):1210-121)

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

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

Significant reduced risk for ischemic stroke in patients with CAD and PAD treated with dual pathway inhibition (Rivaroxaban and Aspirin)



Sharma, M, et al. (Circulation. 2019;139:1134–1145)

PACIFIC Program

Concerted evaluation across phase 2 programs

PACIFIC AF

Atrial fibrillation

20mg asundexian
50mg asundexian
apixaban

~750 patients randomized
Results at ACC 2022

Less bleeding with asundexian 20 or 50 mg QD than with apixaban in patients with AF[1]

PACIFIC AMI

Acute myocardial infarction

10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ dual antiplatelet therapy

~ 1600 patients randomized
Results at ESC 2022

No increase in bleeding on top of dual antiplatelet therapy

PACIFIC STROKE

Non-cardioembolic ischemic stroke

10mg asundexian
20mg asundexian
50mg asundexian
placebo

+ single or dual antiplatelet therapy

~ 1800 patients randomized
Results at ESC 2022

[1]Piccini JP, et al. Lancet 2022; 399: 1383–90

PACIFIC-Stroke study

Objectives:

- To assess the dose-response of 3 different dosages of asundexian compared with placebo on the primary efficacy outcome and, separately, to evaluate the incidence of the primary safety outcomes to determine the dosage that is most efficacious and safe for testing in a phase 3 trial.

Primary Efficacy Outcome:

- The incidence of symptomatic ischemic stroke or covert brain infarcts detected by MRI at 6 months following a non-cardioembolic ischemic stroke for each of the different doses of asundexian and placebo.

Primary Safety Outcome:

- The composite of ISTH[1] major bleeding and clinically relevant non-major bleeding pooled across all asundexian doses and compared to placebo.

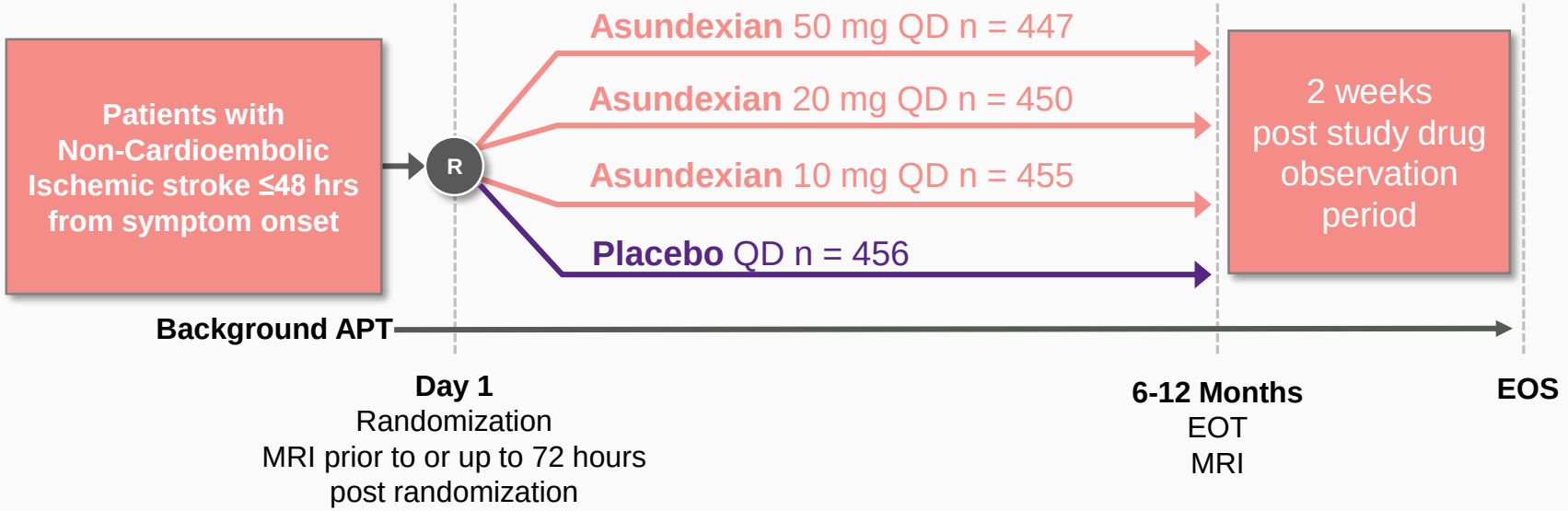
Primary analysis:

- Dose response effect of asundexian on the primary efficacy outcome at 6 months

[1]Schulman, S et al. J Thromb Haemost 2005; 3:692-4

PACIFIC-Stroke: Schema

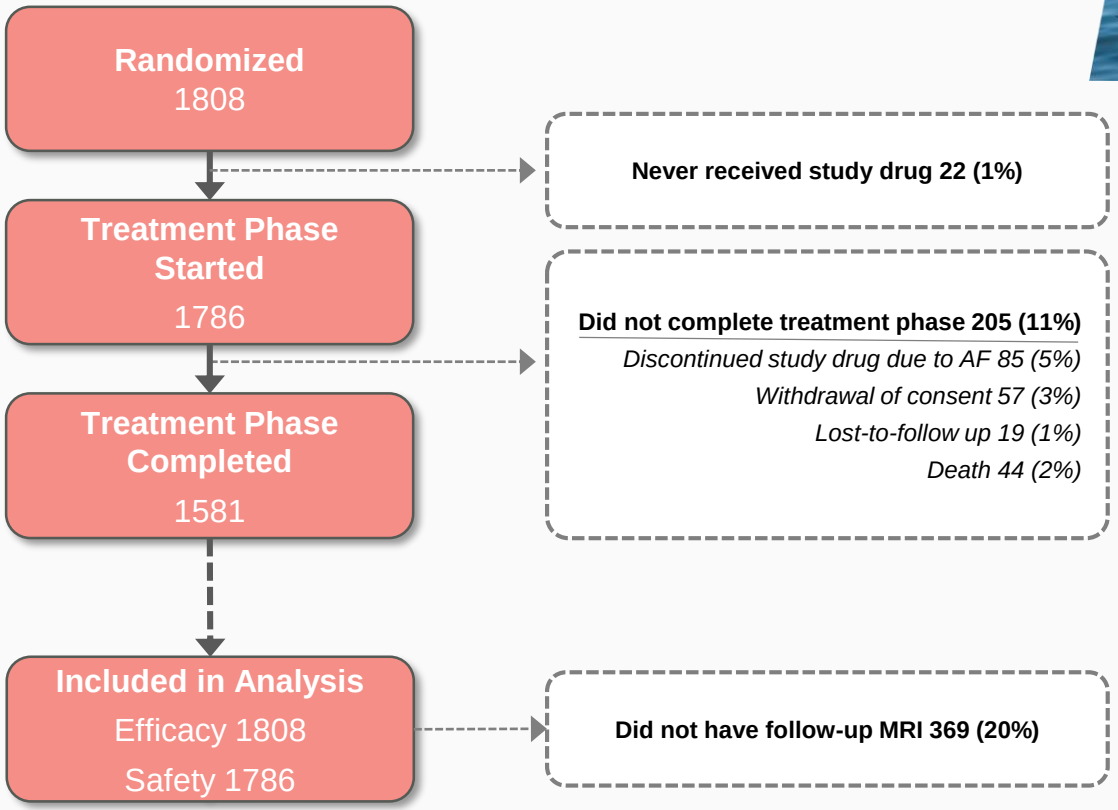
Prospective, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study



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

Results of PACIFIC-Stroke

Study flow


Randomized
1808
Never received study drug 22 (1%)
Treatment Phase Started
1786
Did not complete treatment phase 205 (11%)
Discontinued study drug due to AF 85 (5%)
Withdrawal of consent 57 (3%)
Lost-to-follow up 19 (1%)
Death 44 (2%)
Treatment Phase Completed
1581
Included in Analysis
Efficacy 1808
Safety 1786
Did not have follow-up MRI 369 (20%)

Baseline and Qualifying Stroke Characteristics

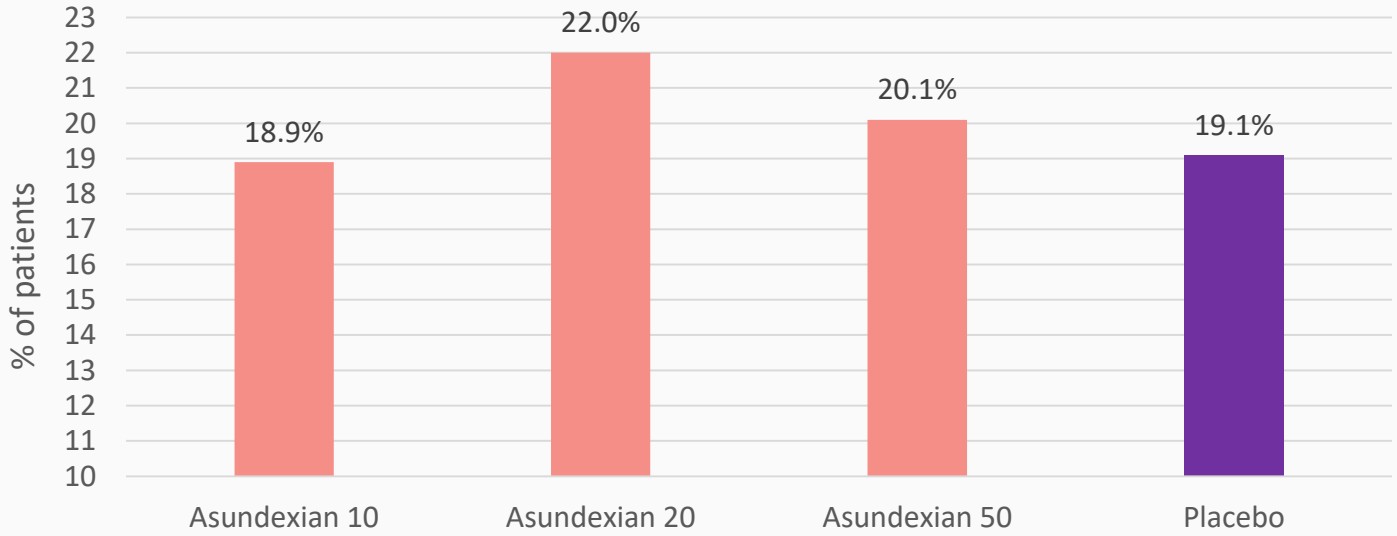
Well Balanced Across Treatment Arms

	All patients (n=1808)
Age (yrs), mean ± SD	67 ±10
Female	34%
Race - White - Asian	83% 15%
Hypertension	77%
Diabetes mellitus	28%
Previous Stroke or TIA	16%
Hours from qualifying stroke to randomization, mean ± SD	36 ±10
Qualifying stroke subtype - Large artery atherosclerosis - Small vessel occlusion - Cryptogenic	 18% 45% 35%
Extra- or intracranial atherosclerosis	34%
NIHSS score at randomization, mean ± SD	3 ± 2
Thrombolysis for index stroke	12%
Initial dual antiplatelet therapy	43%

PACIFIC STROKE

Primary Efficacy Outcome

Ischemic Stroke or Covert Infarcts at 6 months



No observed dose-response (Emax2 model t statistic: -0.68, p=0.80)

Secondary Efficacy Outcome

Incident covert brain infarct(s) on MRI at 6 months (75% of events; 69% small subcortical infarcts)

Outcome	Asundexian, 10 mg (N=455)	Asundexian, 10 mg vs. placebo	Asundexian, 20 mg (N=450)	Asundexian, 20 mg vs. placebo	Asundexian, 50 mg (N=447)	Asundexian. 50 mg vs. placebo	Placebo (N=456)
	No. of patients (%)	CIR (90% CI)	No. of patients (%)	CIR (90% CI)	No. of patients (%)	CIR (90% CI)	No. of patients (%)
Incident covert brain infarct(s) on MRI	63 (13.8%)	**0.99 (0.75 - 1.30)**	74 (16.4%)	**1.17 (0.90 - 1.51)**	74 (16.6%)	**1.17 (0.91 - 1.52)**	64 (14.0%)

No effect on covert brain infarct

Secondary Efficacy Outcomes

Total follow-up (median 10.6 months)

Outcome	Asundexian, 10 (N=455)	Asundexian, 10 vs. placebo	Asundexian, 20 (N=450)	Asundexian, 20 vs. placebo	Asundexian, 50 (N=447)	Asundexian. 50 vs. placebo	Placebo (N=456)
	No. of patients (%)	HR (90% CI)	No. of patients (%)	HR (90% CI)	No. of patients (%)	HR (90% CI)	No. of patients (%)
Ischemic stroke	26 (5.7%)	**0.93 (0.59-1.45)**	26 (5.8%)	**0.94 (0.60-1.47)**	22 (4.9%)	**0.80 (0.50-1.27)**	28 (6.1%)
Any recurrent stroke	26 (5.7%)	**0.86 (0.56-1.34)**	26 (5.8%)	**0.88 (0.56-1.36)**	25 (5.6%)	**0.85 (0.54-1.32)**	30 (6.6%)
Ischemic stroke, vascular death or myocardial infarction	33 (7.3%)	**0.94 (0.63-1.40)**	30 (6.7%)	**0.87 (0.58-1.30)**	33 (7.4%)	**0.96 (0.64-1.43)**	35 (7.7%)
All-cause mortality	10 (2.2%)	**1.00 (0.48-2.09)**	6 (1.3%)	**0.60 (0.26-1.41)**	17 (3.8%)	**1.72 (0.89-3.32)**	10 (2.2%)

Positive trend shown for reduction in ischemic stroke with asundexian 50 mg

Secondary Exploratory Outcomes

Total follow-up (median 10.6 months)

Outcome	Asundexian, 10 (N=455)	Asundexian, 10 vs. placebo	Asundexian, 20 (N=450)	Asundexian, 20 vs. placebo	Asundexian, 50 (N=447)	Asundexian. 50 vs. placebo	Placebo (N=456)
	No. of patients (%)	HR (90% CI)	No. of patients (%)	HR (90% CI)	No. of patients (%)	HR (90% CI)	No. of patients (%)
TIA	10 (2.2%)	**0.91 (0.44-1.87)**	2 (0.4%)	**0.18 (0.05-0.64)**	2 (0.4%)	**0.18 (0.05-0.65)**	11 (2.4%)
Recurrent ischemic stroke or TIA	35 (7.7%)	**0.92 (0.63-1.35)**	28 (6.2%)	**0.74 (0.49-1.12)**	24 (5.4%)	**0.64 (0.41-0.98)**	38 (8.3%)

Secondary Exploratory Outcomes

Total follow-up (median 10.6 months)

Outcome	Asundexian, 10 (N=455)	Asundexian, 10 vs. placebo	Asundexian, 20 (N=450)	Asundexian, 20 vs. placebo	Asundexian, 50 (N=447)	Asundexian. 50 vs. placebo	Placebo (N=456)
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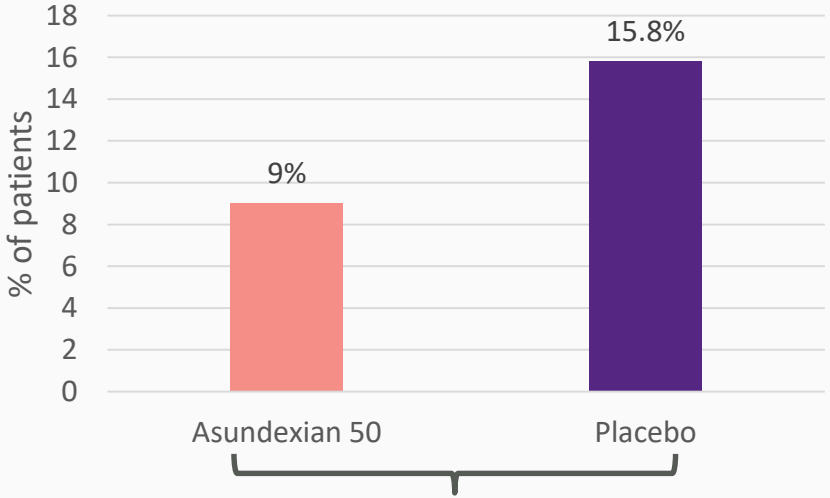
Recurrent ischemic stroke or TIA	35 (7.7%)	**0.92 (0.63-1.35)**	28 (6.2%)	**0.74 (0.49-1.12)**	24 (5.4%)	**0.64 (0.41-0.98)**	38 (8.3%)

Dose dependent reduction of composite of ischemic stroke or TIA with asundexian

Outcome: Recurrent stroke and TIA

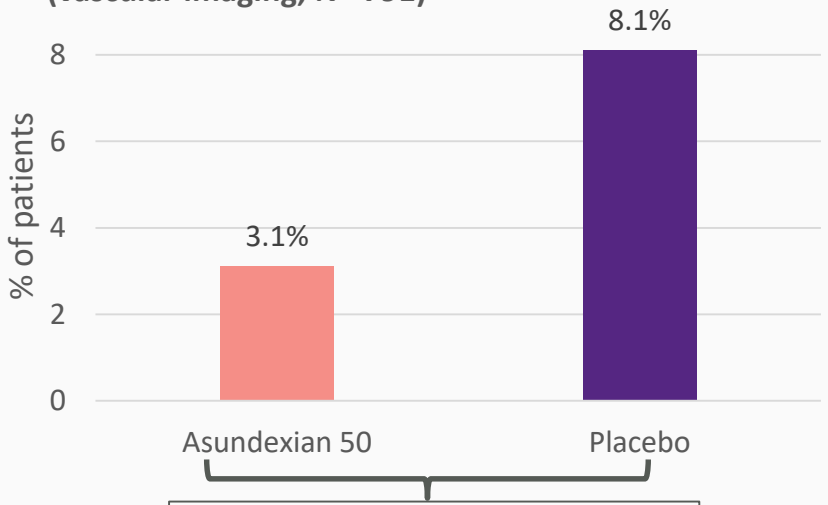
Exploratory post-hoc subgroup analysis

A. Patients with large artery stroke (TOAST, N=320)



HR 0.56, 90% CI 0.26 – 1.19

B. Patients with any extra-/intracranial atherosclerosis (vascular imaging, N= 791)

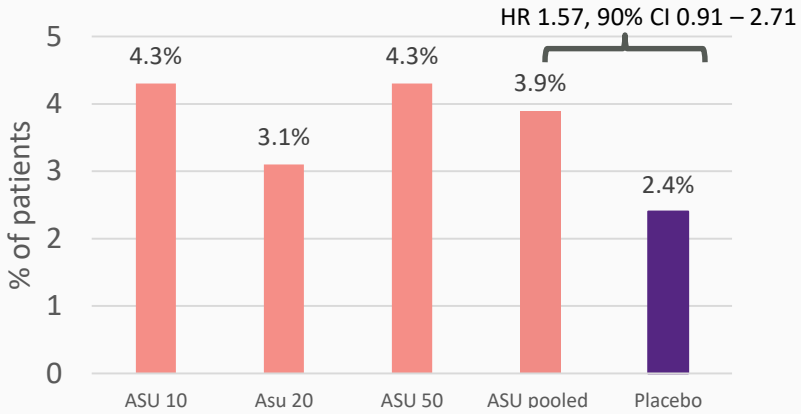


HR 0.39, 90% CI 0.18 – 0.85

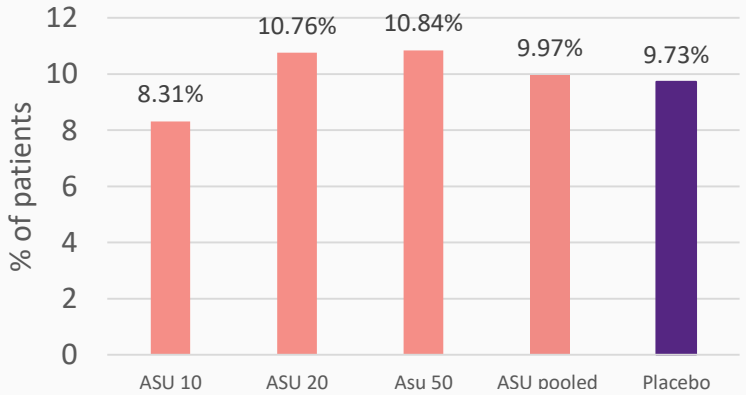
Patients with atherosclerosis had fewer recurrent stroke and TIA with asundexian 50

Bleeding Outcomes

A. Major or Clinically-Relevant Non-Major Bleeding (ISTH)[1]



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	18.4%	17.5%	19.0%	20.6%
PH1 and 2	0.7%	0.2%	0%	0.9%

No significant increase in bleeding and hemorrhagic transformation of index stroke

ASU = Asundexian, HI = hemorrhagic infarct, PH = parenchymal hematoma

[1]Schulman, S et al. J Thromb Haemost 2005; 3:692-4

Conclusions

- **In this phase 2 trial, inhibition of factor XIa with asundexian did not reduce the composite of covert brain infarction or ischemic stroke and no dose response could be shown in patients with acute, non-cardioembolic ischemic stroke.**
  - **Driven by lack of effect on covert brain infarction (largely due to small vessel disease)**
- **Treatment with asundexian 50mg reduced recurrent symptomatic ischemic strokes and TIAs, particularly among those with atherosclerosis**
- **No significant increase in the risk of major or intracranial bleeding with asundexian**
- **The promising results from this phase 2 trial require validation in an adequately-powered phase 3 randomised trial**

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Steering Committee

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Thank you!