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

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Background

- Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation is limited by bleeding concerns.
- Asundexian, a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor, might reduce thrombosis with minimal effect on haemostasis.

AIM of the study

- To determine the optimal dose of asundexian and to compare the incidence of bleeding with that of apixaban in patients with atrial fibrillation.

Methods

- Randomised, double-blind, double-dummy, phase 2 dose-finding study.
- 93 sites in 14 countries, including 12 European countries, Canada, and Japan.
- Asundexian 20 mg or 50 mg once daily was compared with apixaban 5 mg twice daily in patients aged 45 years or older with atrial fibrillation, a CHA2DS2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk.
- Participants were randomly assigned (1:1:1) to a treatment group using an interactive web response system.
- The primary endpoint was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least one dose of study medication.

Results (I)

- 753 patients were included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban).
- The mean age of participants was 73,7 years, 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA2DS2-VASc score was 3,9.
- Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations.
- Asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations.

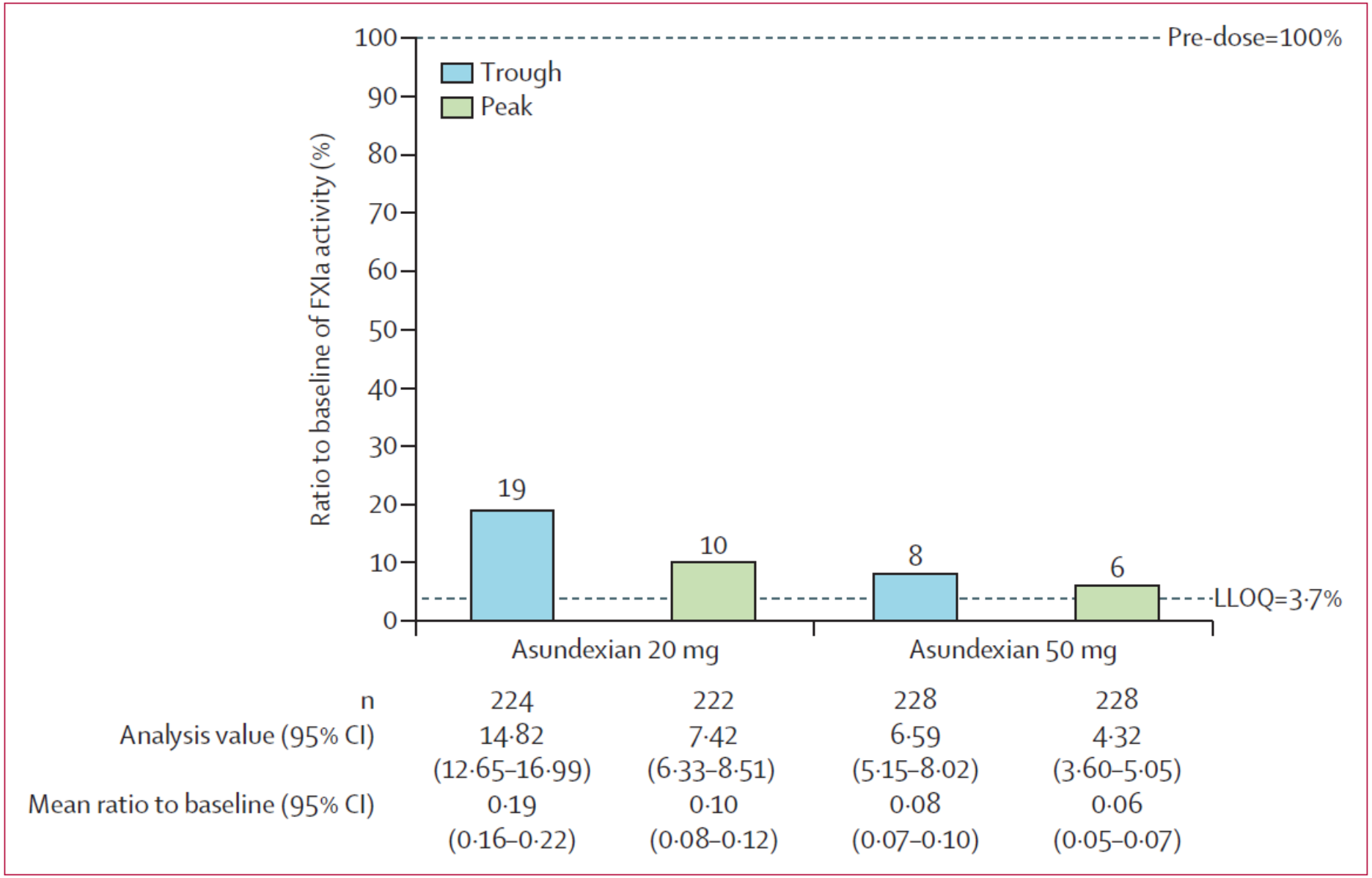

Figure 1: **FXIa activity at steady state after 4 weeks of treatment with asundexian**

Results (II)

- Ratios of incidence proportions for the primary endpoint were 0,50 (90% CI 0,14–1,68) for asundexian 20 mg (three events), 0,16 (0,01–0,99) for asundexian 50 mg (one event), and 0,33 (0,09–0,97) for pooled asundexian (four events) versus apixaban (six events).
- The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.

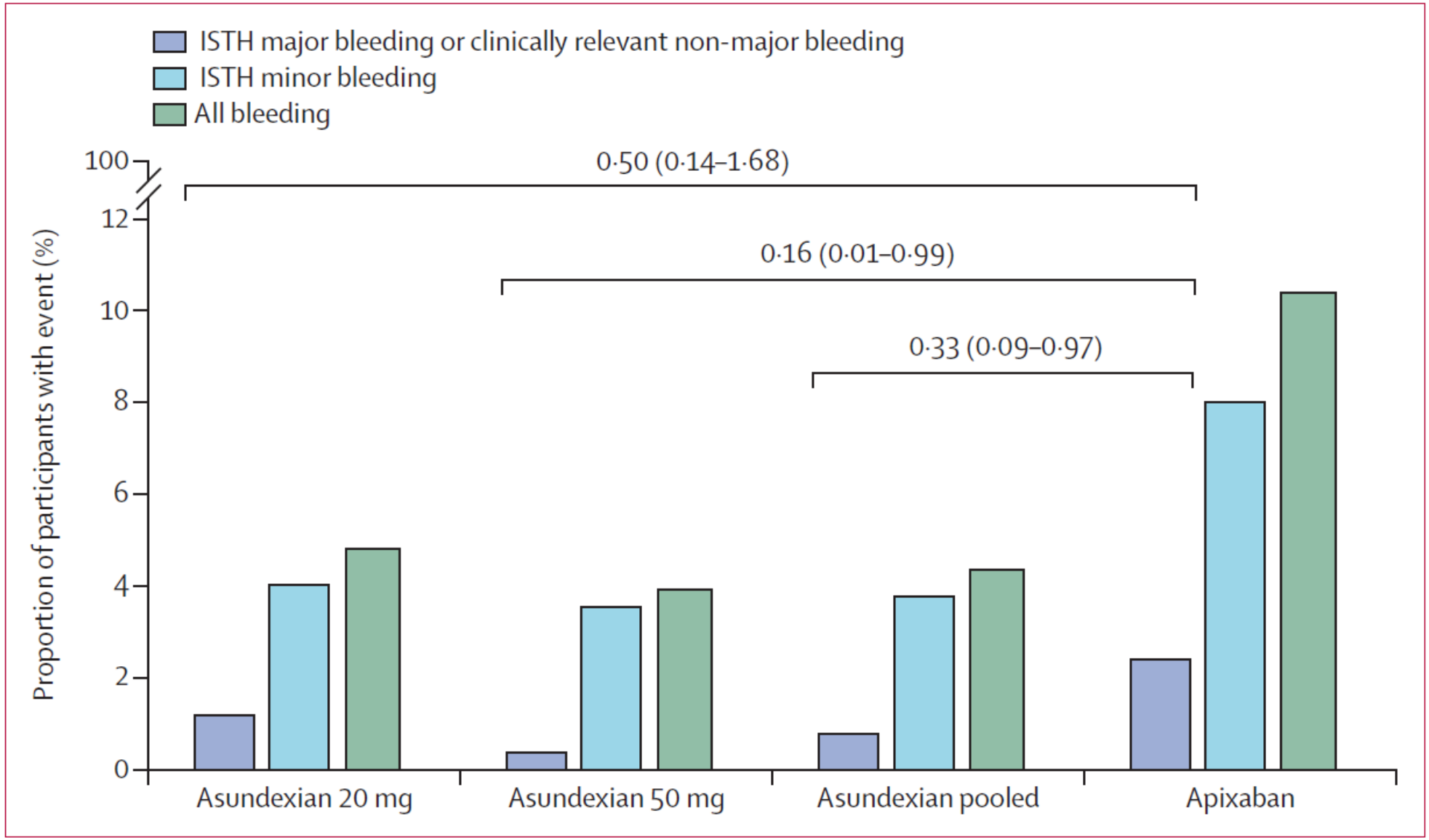

Figure 2: **Safety endpoints according to treatment assignment**

	Asundexian 20 mg (n=249)*	Asundexian 50 mg (n=254)	Apixaban (n=250)	Asundexian total (n=503)	Total (n=753)
Any AE	118 (47%)	120 (47%)	122 (49%)	238 (47%)	360 (48%)
Any study drug-related AE	29 (12%)	26 (10%)	37 (15%)	55 (11%)	92 (12%)
Any AE leading to discontinuation of study drug	15 (6%)	16 (6%)	13 (5%)	31 (6%)	44 (6%)
AE of special interest	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Any SAE	22 (9%)	20 (8%)	20 (8%)	42 (8%)	62 (8%)
Any study drug-related SAE	4 (2%)	0	0	4 (1%)	4 (1%)
Any SAE leading to discontinuation of study drug	4 (2%)	4 (2%)	4 (2%)	8 (2%)	12 (2%)
AE with outcome of death	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Deaths	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Heart failure	0	0	1 (<1%)	0	1 (<1%)
Coronary artery disease	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Sudden cardiac death	0	0	1 (<1%)	0	1 (<1%)
Cerebrovascular accident	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
Completed suicide	0	1 (<1%)	0	1 (<1%)	1 (<1%)

Data are presented as n (%), unless otherwise indicated. AE=adverse event. SAE=serious adverse event. *Table includes only patients who took at least one dose of study drug (two patients did not take study drug).

Table 3: **AEs according to treatment assignment**

Conclusions

- The FXIa inhibitor asundexian at doses of 20 mg and 50 mg once daily resulted in lower rates of bleeding compared with standard dosing of apixaban, with near-complete in-vivo FXIa inhibition, in patients with atrial fibrillation at high bleeding risk.
- Thanks to its safety profile, asundexian might be particularly beneficial and useful early after an ischaemic stroke related to atrial fibrillation.
- The findings in PACIFIC-AF provide reasonable rationale and safety for participant enrolment in a pivotal phase 3 study to determine whether asundexian is superior to current therapy for patient-centred stroke prevention and net clinical benefit.