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# Asundexian in atrial fibrillation: A predictable failure based on pharmacodynamic data?

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## INTRODUCTION

The interruption of the phase 3 OCEANIC-AF trial (NCT05643573) has raised concerns regarding the ability of asundexian, as well as FXI inhibitors in general, to prevent stroke and systematic embolism in patients with atrial fibrillation (AF).

## AIM

To investigate the thrombin generation assay profiles of asundexian, milvexian and apixaban to detect possible pharmacodynamic differences that could explain the results of the OCEANIC-AF trial.

## METHODS

Thrombin Generation Assay (TGA) performed on a Calibrated Automated Thrombogram

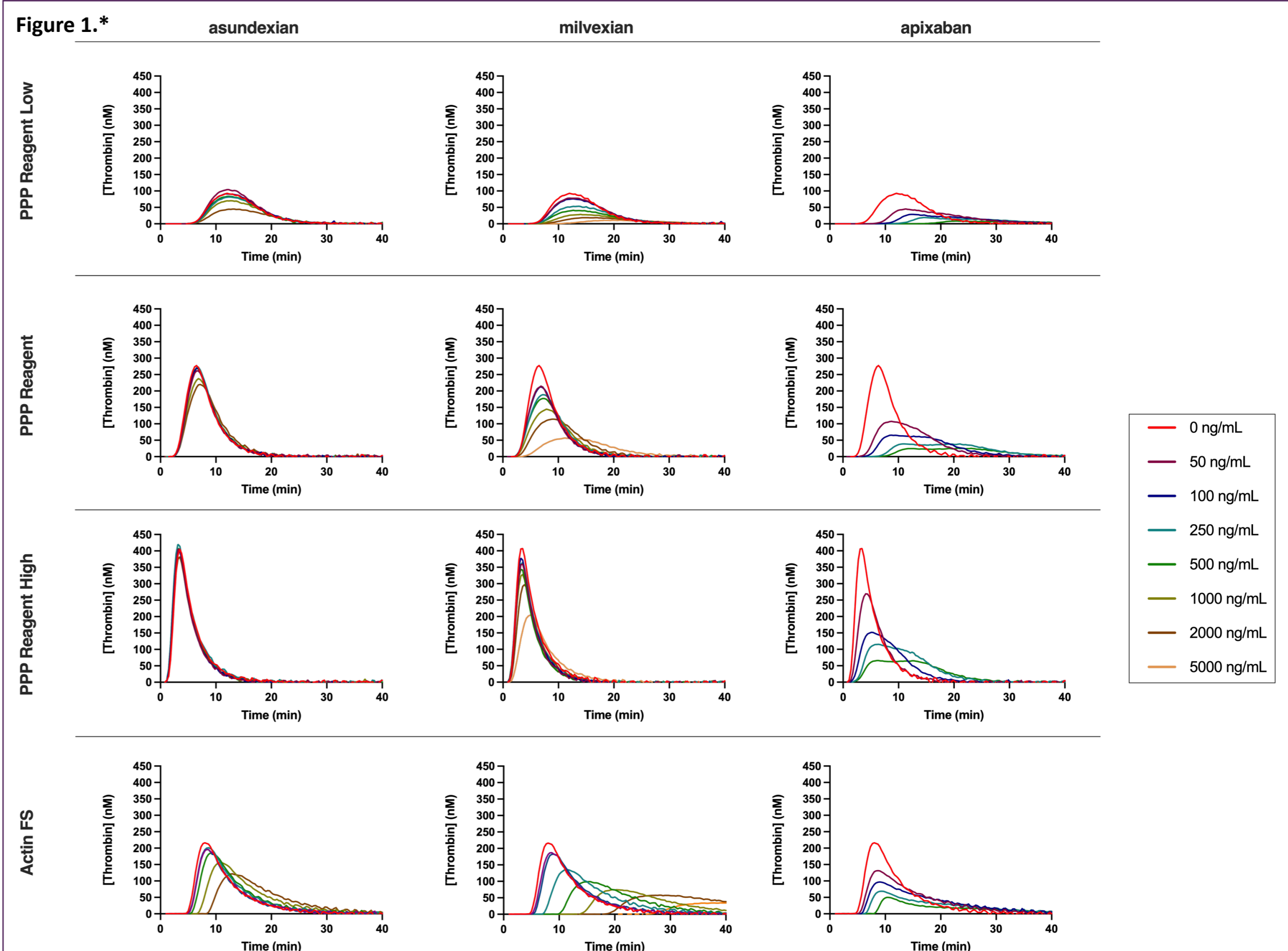
- **20 µL of reagent (final concentrations in wells)**
  - Tissue factor 1 pM, 5 pM or 20 pM + phospholipids 4 µM (PPP Reagent Low, PPP Reagent and PPP Reagent High Stago, respectively)
  - Ellagic acid 0.42 µM + purified soy phosphatides (Actin®FS, Siemens, dilution factor = 40)
- **80 µL of plasma solutions:** asundexian, milvexian and apixaban in PBS without calcium or magnesium spiked (dilution factor = 20) in Normal Pooled Plasma (Namur Exchange Biobank – Nab-X) to yield final concentrations between 0 and 500 ng/mL (apixaban) ; 0 and 2000 ng/mL (asundexian) ; 0 and 5000 ng/mL (milvexian)
- **20 µL of fluorogenic substrate** (amino-methyl-coumarin) and **calcium chloride** in buffer

Statistical analyses: GraphPad Prism software version 10.2.3 (Boston, Massachusetts USA, 2024)

## RESULTS

**Table 1.** Intrapolated IC<sub>50</sub> of ETP and Peak height based on the non-linear relation between the concentrations of inhibitors and the ETP or Peak height values (one-phase decay).

Table 1.	IC <sub>50</sub> ETP (ng/mL) [95% CI]	IC <sub>50</sub> Peak (ng/mL) [95% CI]
asundexian	PPP Low	1876.0 [1598.1 - >2000]
	PPP	>2000
	PPP High	>2000
	Actin FS (F=40)	>2000
milvexian	PPP Low	643.8 [558.2 - 742.4]
	PPP	1893.8 [1633.4 - 2188.7]
	PPP High	>5000
	Actin FS (F=40)	486.0 [435.2 - 542.8]
apixaban	PPP Low	100.3 [80.6 - 124.4]
	PPP	151.1 [130.7 - 174.0]
	PPP High	80.5 [69.3 - 93.5]
	Actin FS (F=40)	80.46 [72.57 - 89.19]



**Figure 1.** TGA curves of asundexian, milvexian and apixaban plasma solutions in the presence of four different reagents

\*Adapted from Vassart, J., Didembourg, M., Morimont, L., Brisbois, C., Jamart, L., Lebreton, A., Mullier, F., Donis, N., Favresse, J., Dogné, J. M., & Douxfils, J. (2024). Asundexian in atrial fibrillation: Can pharmacodynamic data explain the failure?. *Thrombosis research*, 236, 236–239. <https://doi.org/10.1016/j.thromres.2024.03.001>

## DISCUSSION

Asundexian plasma concentration:

- 25 mg and 50 mg (single dose) → C<sub>max</sub> = 358 – 675 ng/mL<sup>[1]</sup>
- 25 mg and 50 mg OD (7 days) → C<sub>max</sub> = 507 – 963 ng/mL<sup>[1]</sup>

Asundexian dose in OCEANIC AF (NCT05643573): 50 mg OD

[1] Kubitzka D, Heckmann M, Distler J, Koechel A, Schweser S, Kanefendt F. Pharm acokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: A randomized phase 1 multiple-dose study. *Br J Clin Pharmacol*. 2022; 88(7): 3447-3462. doi: 10.1111/bcp.15230

[2] V. Perera, Z. Wang, J. Luetzgen, D. Li, M. Desouza, M. Cerra, D. Seiffert, First-in-human study of milvexian, an oral, direct, small molecule factor XIa inhibitor, *Clin. Transl. Sci.* 15 (2) (2022) 330–342. doi: 10.1111/cts.13148

Milvexian plasma concentration

- 60 mg and 200 mg fasted (single dose) → C<sub>max</sub> = 337 - 1068 ng/mL<sup>[2]</sup>
- 200 mg fed (single dose) → C<sub>max</sub> = 1639 ng/mL<sup>[2]</sup>

Milvexian dose in LIBREXIA-AF (NCT05757869): 100 mg b.i.d.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## CONCLUSION

These results confirm that the plasma concentration obtained after the intake of asundexian 50 mg daily is insufficient to inhibit thrombin generation. This may explain the lack of efficacy in patients with AF (OCEANIC AF, NCT05643573).

In comparison, milvexian 100 mg twice daily may be more adequate in this setting.

## CONTACT INFORMATION

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