Efficacy and Safety of the FXIa Inhibitor Milvexian for Secondary Stroke Prevention: Final Results of the AXIOMATIC-SSP Dose-finding Randomized Trial

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<<Sample, final slide will be generated by congress system>>

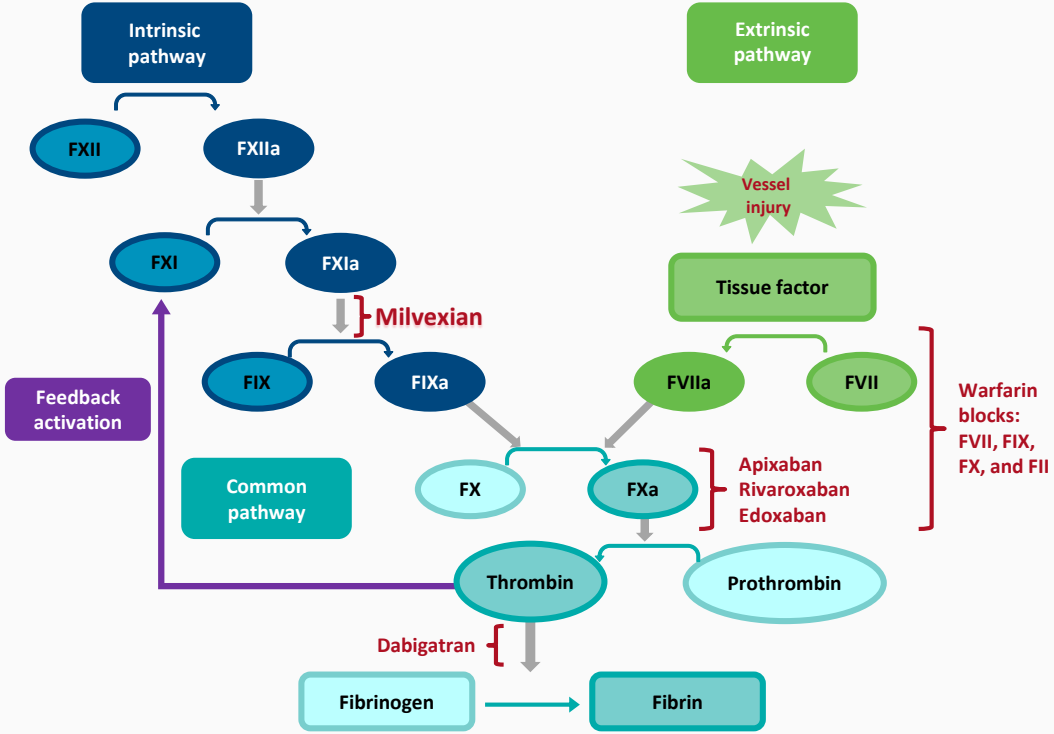
Disclosures

- **Dr. Sharma reports receiving research grants from Bristol Myers Squibb; receiving consulting fees from Janssen, HLS Therapeutics, and Bayer; and is on the board of the Canadian Stroke Consortium**

- **This study was sponsored by Bristol Myers Squibb and Janssen Research & Development, LLC**

Background and Hypothesis

- **Genetically determined FXI deficiency associated with[1,2]**
  - Decrease in ischemic stroke and VTE
  - No increase in ICH
  - Spontaneous bleeding uncommon
- **Factor XI plays a less important role in hemostasis than thrombosis**
  - Activated by FXII and thrombin amplification



FXI, factor XI; VTE, venous thromboembolism; ICH, intracerebral hemorrhage; FXII, factor XII; FXIIa, activated factor XII; FXIa, activated factor XI; FIX, factor IX; FIXa, activated factor IX; FVIIa, activated FVII; FVII, factor VII; FX, factor X; FXa, activated factor X.

1. Solomon O, et al. *Blood.* 2008;111(8):4113-4117. 2. Preis M, et al. *Blood*. 2017;129(9):1210-1215.

Milvexian

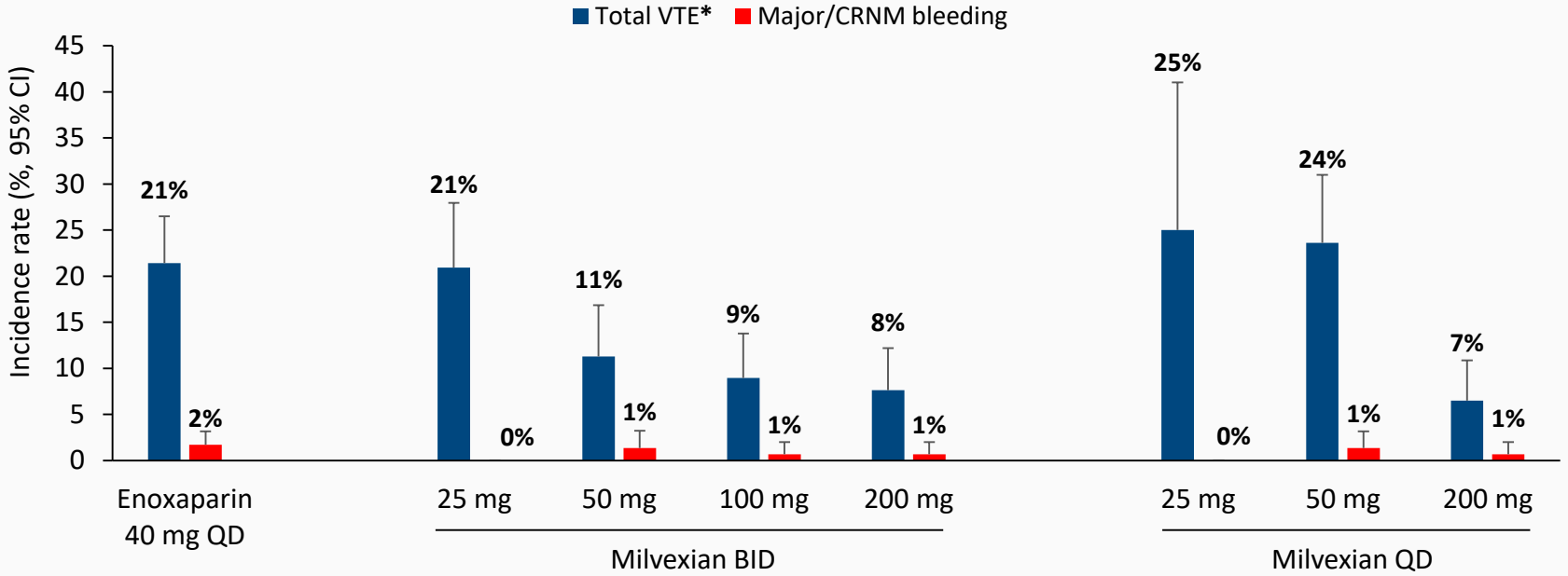
- Potent and specific small-molecule inhibitor of FXIa[1]
- Rapid absorption after oral administration (T_{max} of 2-4 hours)[2]
- Terminal half-life of 11 to 18 hours when administered as multiple doses in healthy volunteers[2]
- Metabolized in the liver primarily by CYP3A4
- Less than 20% eliminated in the urine in healthy subjects*
- Limited drug-drug interaction potential[3-5]

*With spray dried dispersion formulation[2]

T_{max}, time to maximum concentration; CYP3A4, cytochrome P450 enzyme.

1. Dilger AK, et al. *J Med Chem*. 2022;65(3):1770-1785. 2. Perera V, et al. *Clin Transl Sci*. 2022;15(2):330-342. 3. Perera V, et al. *Cardiol Ther*. 2022. doi: 10.1007/s40119-022-00266-6. 4. Perera V, et al. Presented at ASCPT 2021. 5. Perera V, et al. Presented at ESC 2022.

Milvexian Phase 2 Total Knee Replacement Study



RR (95% CI) vs Enoxaparin								
	Total VTE*	0.97 (0.65, 1.45)	0.53 (0.31, 0.90)	0.42 (0.23, 0.76)	0.37 (0.19, 0.69)	1.00 (0.51, 1.97)	1.15 (0.78, 1.70)	0.30 (0.15 0.62)
	Major/CRNM bleeding	0 (NA)	0.79 (0.16, 3.96)	0.39 (0.05, 3.30)	0.39 (0.05, 3.28)	0 (NA)	0.68 (0.14, 3.39)	0.40 (0.05, 3.34)

*Composite of asymptomatic deep-vein thrombosis, confirmed symptomatic venous thromboembolism, or death from any cause.
CRNM, clinically relevant nonmajor; CI, confidence interval; QD, once daily; BID, twice daily; RR, relative risk; NA, not applicable.

1 . Weitz JI, et al. *N Engl J Med*. 2021;385(23):2162-2172.

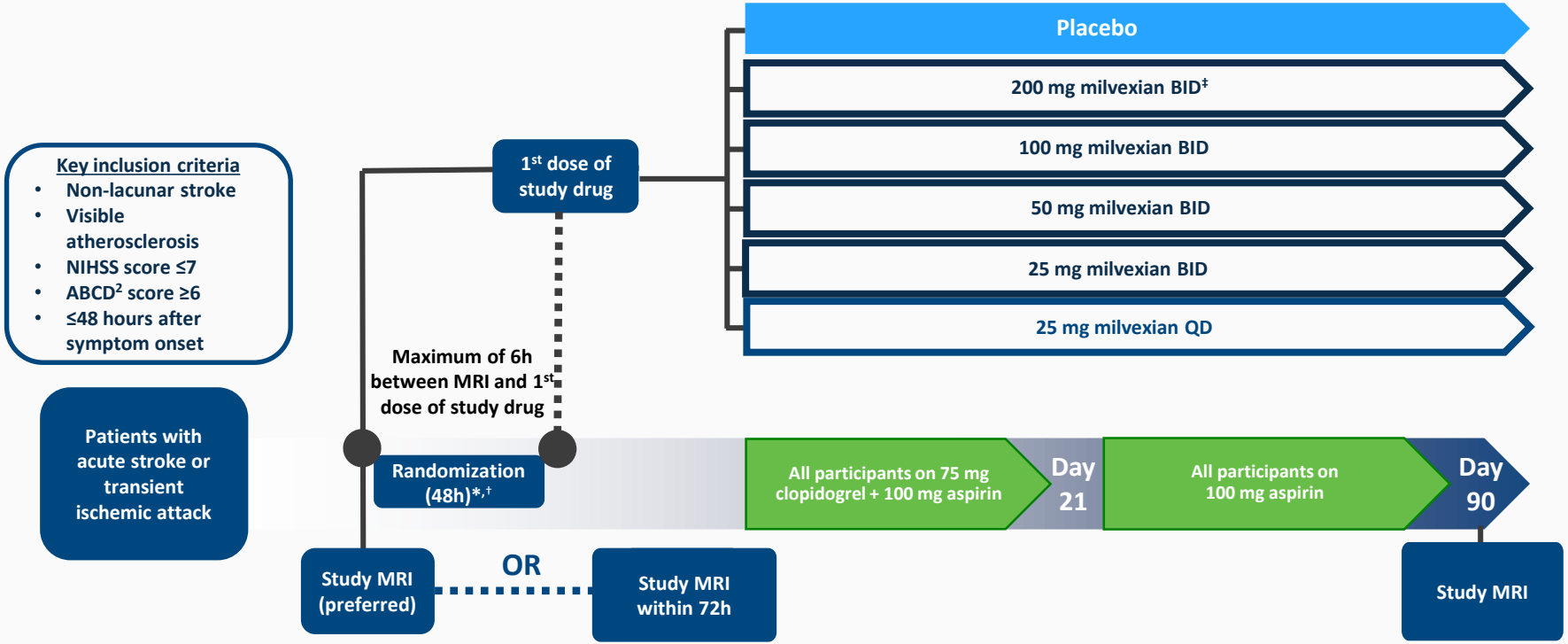
AXIOMATIC-SSP Key Objectives and Endpoints

Objectives	Endpoints
Primary	
To estimate the dose-response relationship of milvexian in participants with ischemic stroke or TIA	Composite of: 1. New ischemic stroke between Day 1 and Day 90 2. New covert brain infarction on MRI at Day 90 (MRI assessed by central review)*
Secondary	
To assess the rate of major bleeding after treatment with milvexian versus placebo	Event rate classified according to Bleeding Academic Research Consortium (BARC) Type 3 and 5

The study is powered to detect the dose-response relationship; it is not powered to detect the risk difference in the primary outcome for each milvexian dose group versus placebo.

*Fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequence.
TIA, transient ischemic attack; MRI, magnetic resonance imaging.

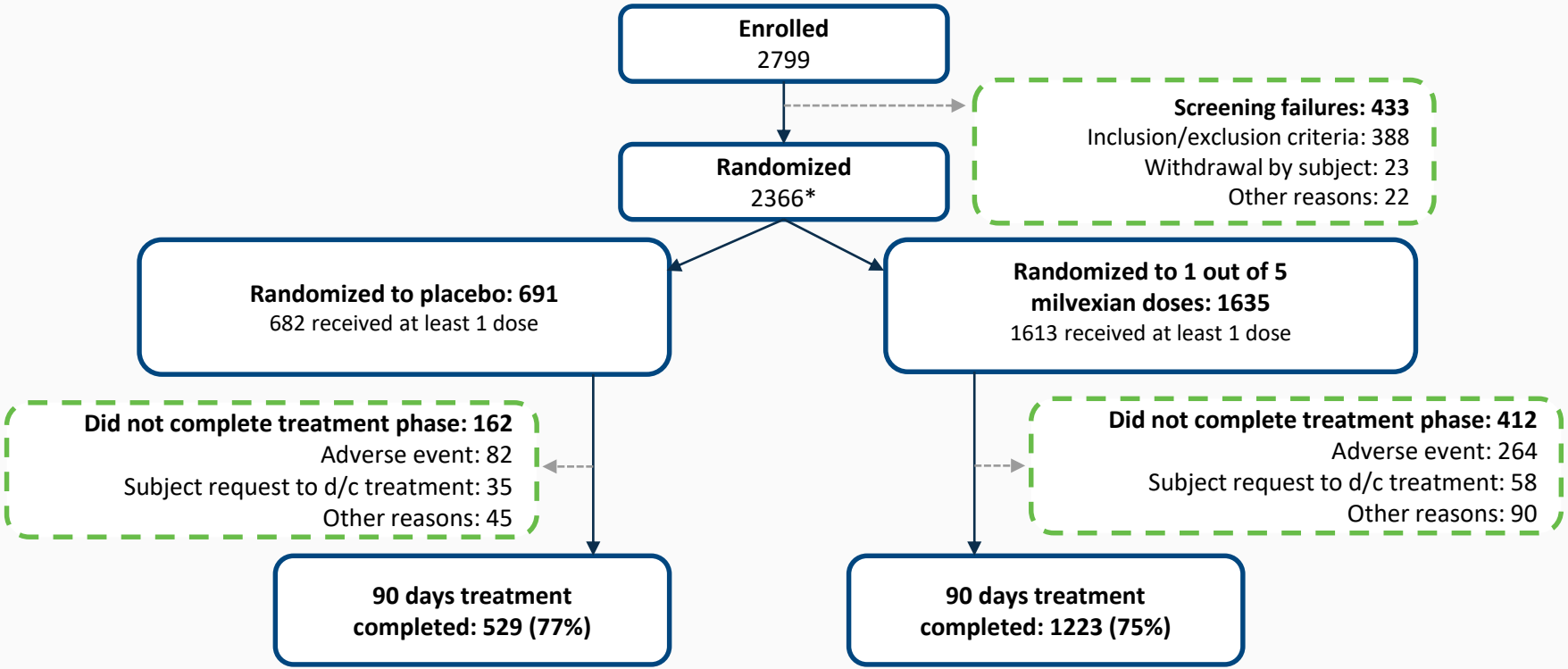
AXIOMATIC-SSP Study Design



*300 mg clopidogrel LD + 100 mg aspirin. †600 mg clopidogrel LD permitted. ‡The milvexian 200 mg BID cohort (2:1 ratio of milvexian to placebo) was added after 450 participants from the lower doses completed the Day 21 visit.

NIHSS, National Institutes of Health Stroke Scale; ABCD², age, blood pressure, clinical features, duration of TIA, and presence of diabetes.

Disposition/Study Flow



*40 subjects were randomized to 50 mg QD/100 mg QD dosing arms that were terminated early and the data were not considered for further analysis.
d/c, discontinue.

Participant Demographics*

	Placebo (n = 691)	Milvexian				
		QD regimen	BID regimen			
		25 mg (n = 328)	25 mg (n = 318)	50 mg (n = 328)	100 mg (n = 310)	200 mg (n = 351)
Age, years, median **Aged ≥75 years, %**	70.0 33	72.0 39	71.5 39	70.0 34	70.5 36	71.0 35
Female sex, %	37	33	37	37	36	36
Hypertension, %	79	78	75	77	78	76
Diabetes mellitus, %	32	31	32	27	31	30
Hypercholesterolemia, %	58	59	55	59	62	64
Smoking, %	54	53	47	50	54	54

*Intent-to-Treat (ITT) Population=Includes all participants who were randomized to a treatment, regardless receiving study drug or not

Participant Clinical Characteristics*

	Placebo (n = 691)	Milvexian				
		QD regimen	BID regimen			
		25 mg (n = 328)	25 mg (n = 318)	50 mg (n = 328)	100 mg (n = 310)	200 mg (n = 351)
Qualifying event, %						
Ischemic stroke	76	73	75	77	74	79
TIA	24	27	24	23	26	21
NIHSS for stroke qualifying event, median	2	2	2	2	2	2
Time from symptom onset to 1st dose, hours, median	35	36	37	33	34	36

*ITT Population=Includes all participants who were randomized to a treatment, regardless receiving study drug or not

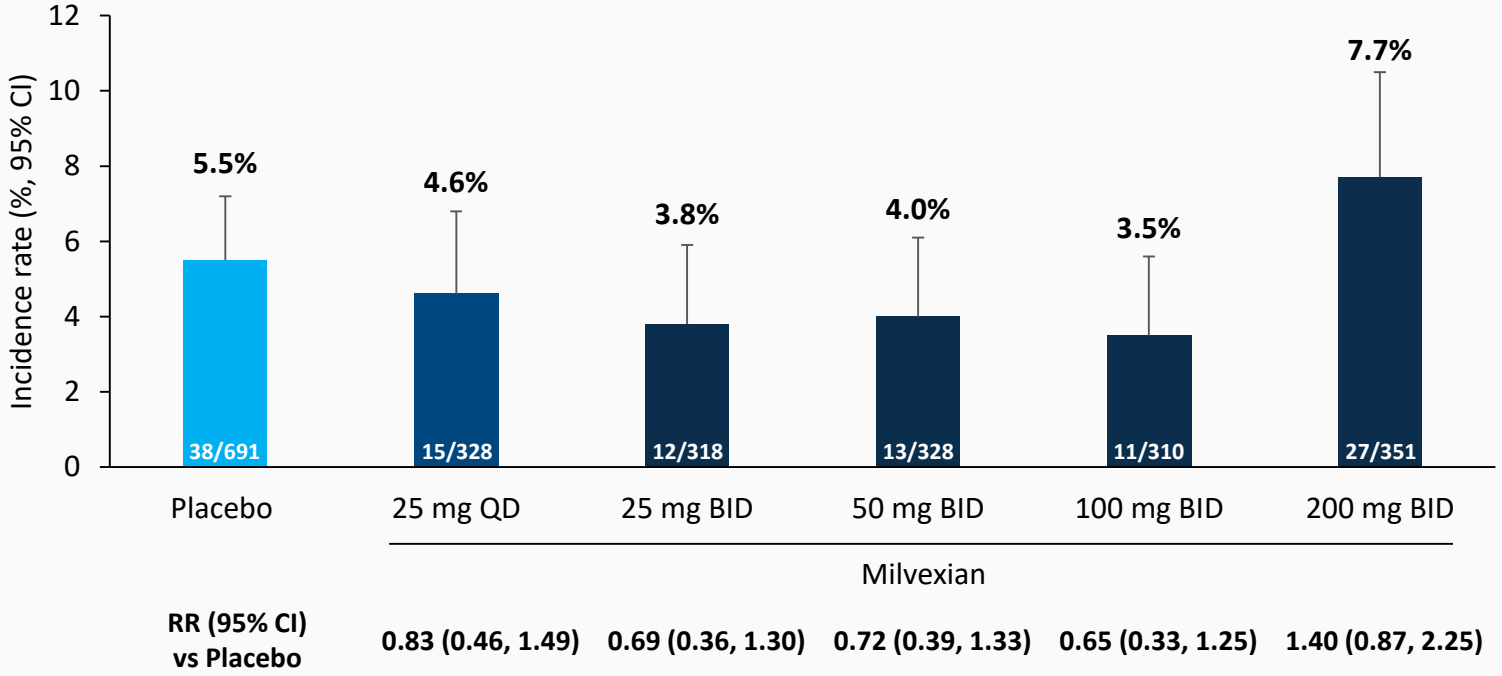
Primary Endpoint and Components*

	Placebo (n = 625)	Milvexian				
		QD regimen	BID regimen			
		25 mg (n = 308)	25 mg (n = 287)	50 mg (n = 306)	100 mg (n = 277)	200 mg (n = 317)
Subjects with composite event, %	16.6	16.2	18.5	14.1	14.8	16.4
Symptomatic ischemic stroke	6.1	4.9	4.2	4.2	4.0	8.5
Covert infarcts	10.6	11.4	14.3	9.8	10.8	7.9
****Model-based estimate for composite event (95% CI)**	16.8 (14.1, 19.4)	16.7 (14.4, 19.0)	16.6 (14.5, 18.7)	15.6 (13.6, 17.8)	15.4 (13.0, 18.0)	15.3 (12.4, 20.5)
Relative risk (95% CI)	–	0.99 (0.87, 1.10)	0.99 (0.84, 1.16)	0.93 (0.76, 1.17)	0.92 (0.73, 1.19)	0.91 (0.70, 1.32)

*Evaluable Population=Includes all randomized participants with a Day 90 MRI

** Multiple Comparison Procedure – Modelling (MCP-MOD) dose-response relationship of Milvexian

Symptomatic Ischemic Stroke*



- No hemorrhagic strokes occurred

*ITT Population=Includes all participants who were randomized to a treatment, regardless receiving study drug or not

Adverse Events*

	Placebo (n = 682)	Milvexian				
		QD regimen	BID regimen			
		25 mg (n = 325)	25 mg (n = 313)	50 mg (n = 325)	100 mg (n = 306)	200 mg (n = 344)
AE, n (%)	399 (58.5)	190 (58.5)	186 (59.4)	192 (59.1)	193 (63.1)	211 (61.3)
SAE, n (%)	94 (13.8)	37 (11.4)	39 (12.5)	41 (12.6)	42 (13.7)	54 (15.7)
Bleeding AE, n (%)	66 (9.7)	31 (9.5)	27 (8.6)	48 (14.8)	41 (13.4)	42 (12.2)
Discontinuation due to AE, n (%)	83 (12.2)	44 (13.5)	47 (15.0)	46 (14.2)	51 (16.7)	79 (23.0)
Death, n (%)	0	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	0

*All Treated Participants=Includes all participants who received at least one dose of study medication
AE, adverse event; SAE, serious adverse event.

Bleeding by BARC Type*

	Placebo (n = 682)	Milvexian				
		QD regimen	BID regimen			
		25 mg (n = 325)	25 mg (n = 313)	50 mg (n = 325)	100 mg (n = 306)	200 mg (n = 344)
All BARC Types, n (%)	**54 (7.9)**	**35 (10.8)**	**27 (8.6)**	**40 (12.3)**	**40 (13.1)**	**35 (10.2)**
Type 1: Not actionable	41 (6.0)	26 (8.0)	16 (5.1)	28 (8.6)	25 (8.2)	22 (6.4)
Type 2: Requiring assessment/treatment	9 (1.3)	7 (2.2)	9 (2.9)	7 (2.2)	10 (3.3)	8 (2.3)
Type 3a: Hgb drop 3-5 g/dL or transfusion	2 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	3 (0.9)
Type 3b: Hgb drop ≥5 g/dL or requiring surgical intervention	0	1 (0.3)	1 (0.3)	1 (0.3)	3 (1.0)	1 (0.3)
Type 3c: Intracranial hemorrhage including symptomatic HT	**2 (0.3)**	**0**	**0**	**3 (0.9)**	**0**	**1 (0.3)**
Type 4: CABG-related	0	0	0	0	0	0
Type 5: Fatal	**0**	**0**	**0**	**0**	**0**	**0**

*All Treated Participants=Includes all participants who received at least one dose of study medication
Hgb, hemoglobin; HT, hemorrhagic transformation; CABG, coronary artery bypass grafting.

BARC Type 3 and 5 Bleeding*

	Placebo (n = 682)	Milvexian				
		QD Regimen	BID Regimen			
		25 mg (n = 325)	25 mg (n = 313)	50 mg (n = 325)	100 mg (n = 306)	200 mg (n = 344)
Composite event rate, n (%) [95% CI]	4 (0.6) [0.2, 1.5]	2 (0.6) [0.1, 2.2]	2 (0.6) [0.1, 2.3]	5 (1.5) [0.5, 3.6]	5 (1.6) [0.5, 3.8]	5 (1.5) [0.5, 3.4]
Components, n (%)						
BARC Type 3	4 (0.6)	2 (0.6)	2 (0.6)	5 (1.5)	5 (1.6)	5 (1.5)
BARC Type 5	0	0	0	0	0	0
Risk difference vs placebo (95% CI)	–	0.03 (–1.03, 1.72)	0.05 (–1.02, 1.81)	0.95 (–0.35, 3.06)	1.05 (–0.30, 3.27)	0.87 (–0.41, 2.86)
Relative risk vs placebo (95% CI)	–	1.05 (0.14, 5.89)	1.09 (0.15, 6.11)	2.62 (0.64, 11.75)	2.79 (0.68, 12.47)	2.48 (0.60, 11.09)

*All Treated Participants=Includes all participants who received at least one dose of study medication

Conclusions

- **Efficacy**
  - No dose response for the primary composite endpoint (symptomatic ischemic stroke + covert brain infarction)
  - Milvexian was associated with fewer symptomatic ischemic strokes at all doses except 200 mg BID:
    - Doses from 25 mg to 100 mg BID showed similar relative risk reduction for symptomatic ischemic stroke at approximately 30% versus placebo
- **Bleeding**
  - Major bleeding: The incidence of major bleeding was low (0.6%-1.6%)
    - Numerical increases in major bleeding (BARC Type 3) at milvexian doses of 50 mg BID and above; the majority were GI bleeds
    - No increase in symptomatic ICH bleeding (BARC Type 3c) versus placebo
    - No fatal bleeding (BARC Type 5)

GI, gastrointestinal.

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