Andexanet alfa in Factor Xa Inhibitor-Associated Acute Major Bleeding

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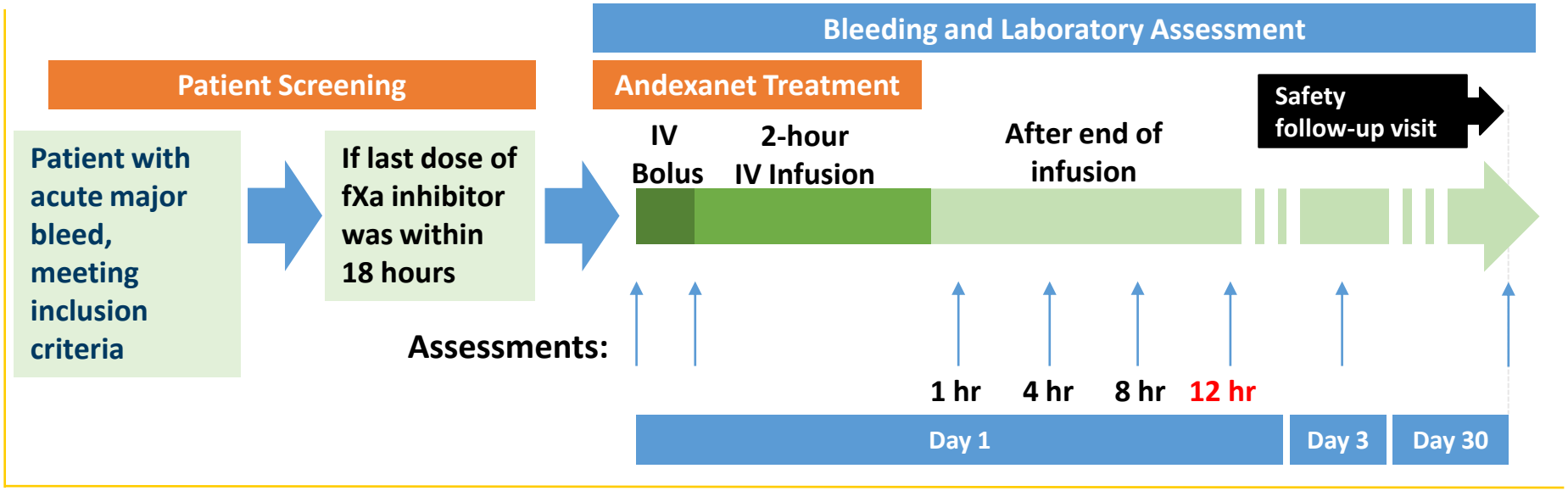
- on behalf of the ANNEXA-4 investigators

Declaration of Interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Portola Pharmaceutical
- Bayer AG
- Bristol Myers Squibb
- Pfizer
-)

ANNEXA-4 Study Design



Primary Efficacy Measurements

- Change in anti-FXa activity
- Clinical hemostatic efficacy through 12 hours
  - independent adjudication committee
  - pre-specified precise evaluation criteria

Safety Measurements

- Overall safety
- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day all-cause mortality

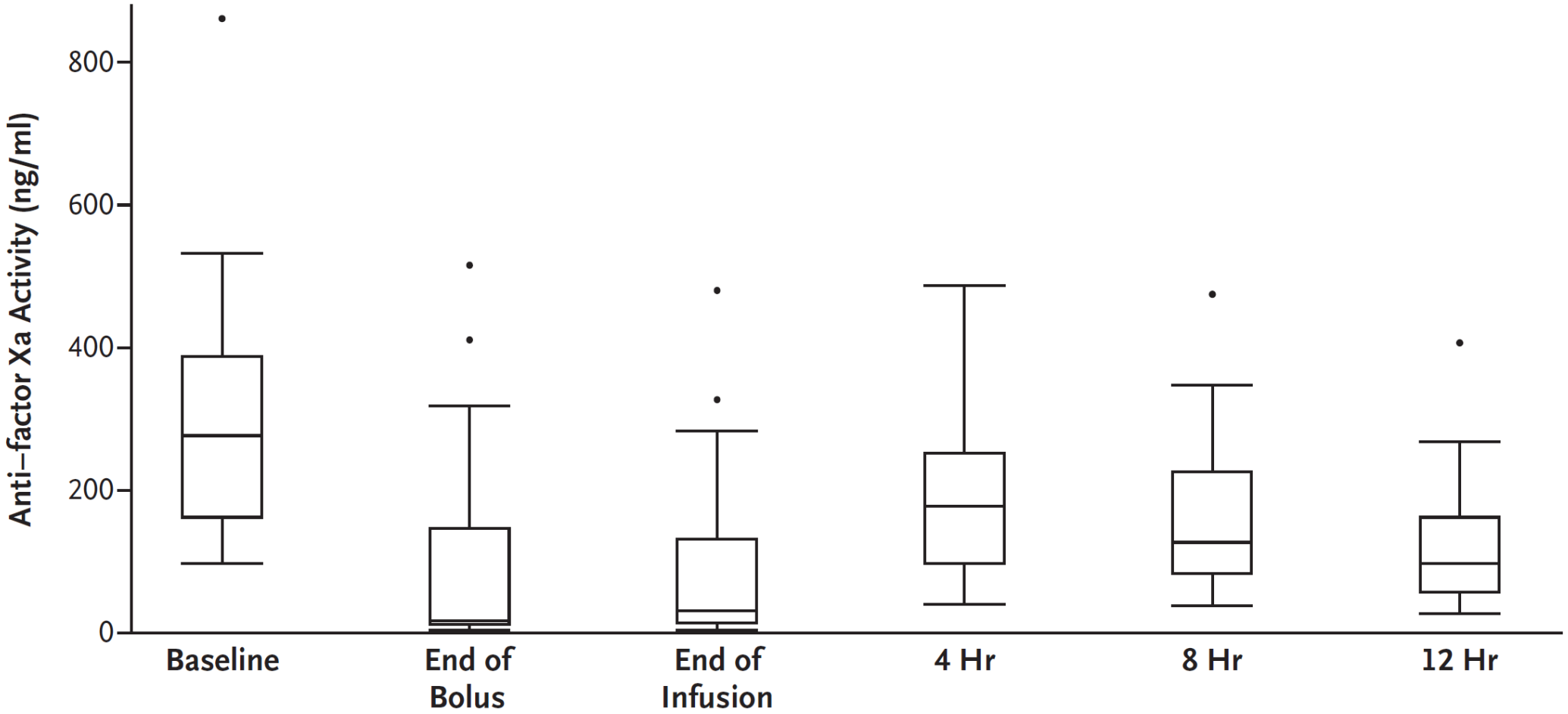
Baseline Characteristics

	Safety Population N=67	Efficacy Population N=47
Age (yr), mean ± SD	77.1 (10.00)	77.1 (10.08)
Male, n (%)	35 (52.2)	24 (51.1)
White race, n (%)	54 (80.6)	36 (76.6)
Time from presentation until andexanet bolus (hrs), mean ± SD	4.8 ± 1.93	4.8 ± 1.82
Estimated creatinine clearance < 30 mL/min, n (%)	6 (9.0)	4 (8.5)
Indication for anticoagulation		
Atrial fibrillation, n (%)	47 (70.1)	32 (68.1)
VTE *, n (%)	15 (22.4)	12 (25.5)
Atrial fibrillation and VTE *, n (%)	5 (7.5)	3 (6.4)
Medical History		
Myocardial infarction, n (%)	13 (19.4)	7 (14.9)
Stroke, n (%)	17 (25.4)	15 (31.9)
Deep vein thrombosis, n (%)	20 (29.9)	16 (34.0)
Pulmonary embolism, n (%)	6 (9.0)	4 (8.5)
Atrial Fibrillation, n (%)	49 (73.1)	34 (72.3)
Heart Failure, n (%)	23 (34.3)	19 (40.4)
Diabetes mellitus, n (%)	23 (34.3)	17 (36.2)

Site of Bleeding

	Safety Population N=67	Efficacy Population N=47
Gastrointestinal Bleeding, n (%)	**33 (49.3)**	**25 (53.2)**
Upper, n (%)	9 (27.3)	7 (28.0)
Lower, n (%)	10 (30.3)	8 (32.0)
Unknown, n (%)	14 (42.4)	10 (40.0)
Intracranial Bleeding, n (%)	**28 (41.8)**	**20 (42.6)**
Glasgow Coma Scale, mean ± SD	14.1 ± 1.69	14.1 ± 1.72
Intracerebral site, n (%)	14 (50.0)	12 (60.0)
Sub-dural site, n (%)	11 (39.3)	7 (35.0)
Subarachnoid site, n (%)	3 (10.7)	1 (5.0)
Other Bleeding site, n (%)	**6 (9.0)**	**2 (4.3)**
Nasal, n (%)	1 (16.7)	0 (0.0)
Pericardial/pleural/retroperitoneal, n (%)	3 (50.0)	1 (50.0)
Genital/urinary, n (%)	1 (16.7)	1 (50.0)
Articular, n (%)	1 (16.7)	0 (0.0)

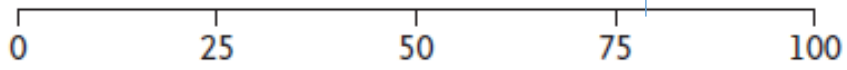
Anti-factor Xa Activity: Rivaroxaban n= 26



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	277.0	16.8	30.6	177.7	127.1	97.9
Percent Change (95% CI)		–89 (–58 to –94)	–86 (–55 to –93)	–39 (–27 to –45)	–49 (–43 to –57)	–64 (–51 to –70)

Clinical Hemostatic Efficacy

Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)



Safety Assessment

- Anticoagulation re-started in 18 patients (27%) by 30 days
- Thrombotic events occurred within 3 days of andexanet in 4 (6%) patients and by 30 days in 12 (18%)
- Therapeutic anticoagulation was re-started in only 1 patient before a thrombotic event occurred
- 10 deaths occurred by 30 days (15%), of which 6 were cardiovascular

Conclusions

- Andexanet bolus plus 2 hour infusion rapidly reversed anti-fXa activity
- Effective hemostasis observed in 79% of patients
- Thrombotic events occurred at rates consistent with the high risk profile of the patients