



Cardiovascular and Renal Drugs Advisory Committee

September 8, 2011

NDA 202439 **Dose Selection**

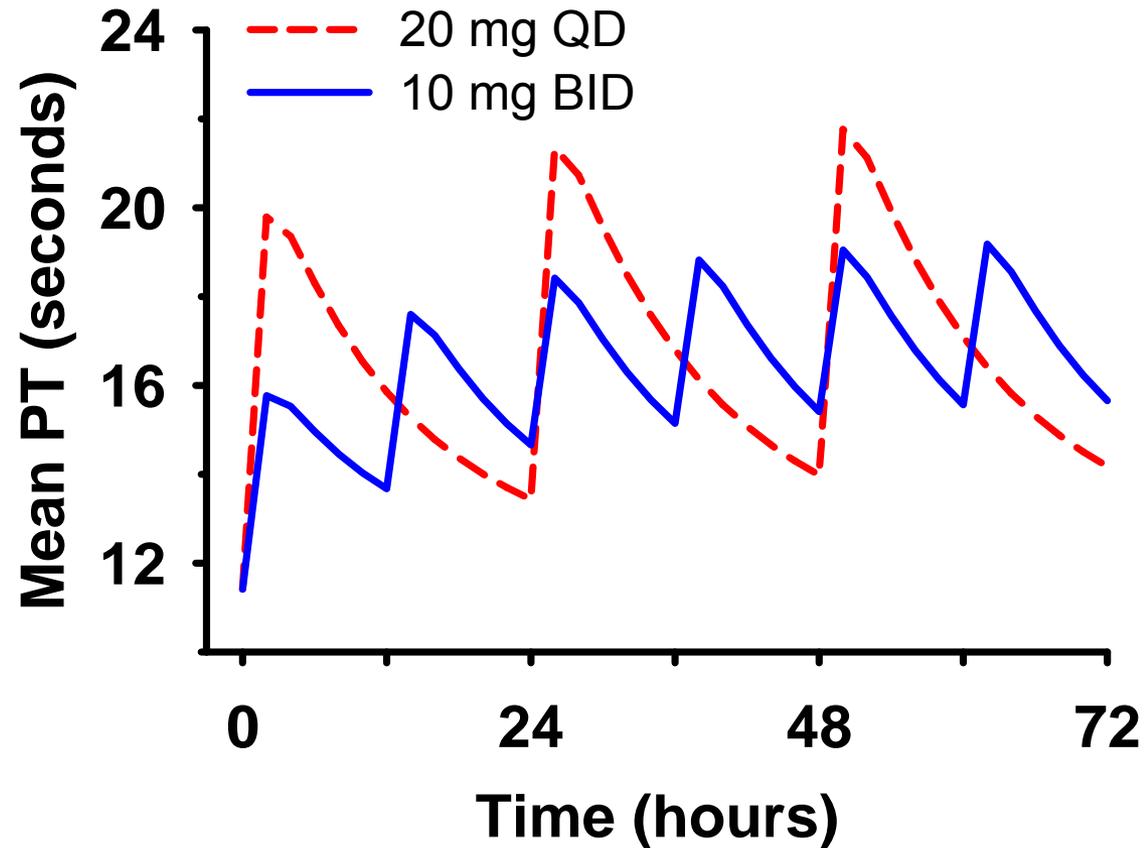
Preston Dunnmon, MD, MBA, FACP, FACC
Clinical Reviewer
Division of Cardiovascular and Renal Products

Dose Selection for ROCKET

- PK-PD Profile
- VTE Treatment Studies
- ATLAS ACS 1 TIMI 46
- ROCKET PK-PD-Outcomes
 - PT as a surrogate for exposure
 - Exposure driven efficacy and safety analyses

BID regimen has lower PT fluctuation compared to QD regimen

- $t_{1/2}$ of 5-9 h in healthy, 11-13 h in elderly
- Minimal PT effect in the 2nd half of the inter-dosing interval with QD dosing



Phase II VTE Studies

- No dose ranging studies in atrial fibrillation patients
- ROCKET dose based on two small Phase 2 VTE treatment studies
 - 20 mg/day lowest total daily dose given in either study
 - Small number of outcome events
 - Neither study demonstrated efficacy dose response
 - Only 11223 tested same total daily dose given QD and BID
 - Better efficacy with BID dosing
 - Numerically fewer non-major bleeding events with BID dosing

BID vs. QD for Efficacy in DVT

	Rivaroxaban				Enox/ VKA (N = 109)
Overall response at Week 12	10 mg bid (N = 100)	20 mg bid (N = 98)	40 mg qd (N = 112)	30 mg bid (N = 109)	
Improved	53 (53%)	58 (59%)	49 (44%)	62 (57%)	50 (46%)
Unchanged	46 (46%)	39 (40%)	63 (56%)	47 (43%)	59 (54%)

Study 11223 primary efficacy endpoint: response to treatment (i.e., thrombus regression) as determined by compression ultrasound (CUS, 4 pt reduction) at day 21, with symptomatic recurrence of DVT, PE, or VTE-related death to day 21 defined as negative response regardless of CUS score

BID vs. QD for Bleeding in DVT

	Rivaroxaban				Enox/ VKA (N = 126)
	10 mg bid (N = 119)	20 mg bid (N = 117)	40 mg qd (N = 121)	30 mg bid (N = 121)	
Any bleeding event	6 (5.0%)	11 (9.4%)	14 (11.6%)	13 (10.7%)	8 (6.3%)
Major Bleeding	2 (1.7%)	2 (1.7%)	2 (1.7%)	4 (3.3%)	0 (0.0%)

Study 11223 primary safety endpoint: incidence of treatment-emergent major bleeding events (fatal bleeding, clinically overt bleeding associated with a fall in hemoglobin level of ≥ 2 g/dL, clinically overt bleeding leading to transfusion of ≥ 2 units of packed cells or whole blood, and bleeding into critical organ)

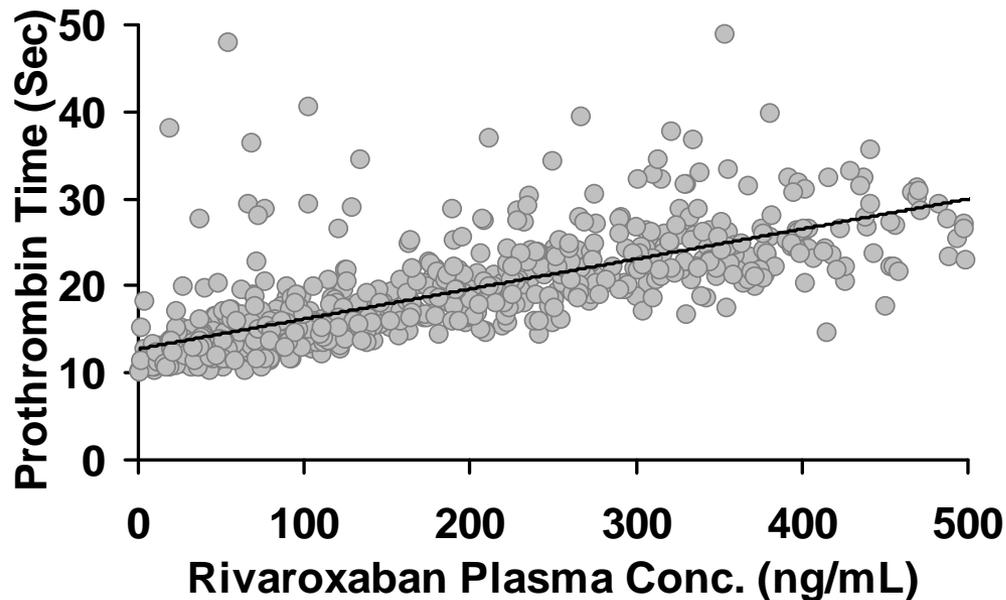
ATLAS ACS 1 TIMI 46 Bleeding Events

Total Daily Dose	Pooled placebo KM rate (n/N)	Once daily dosing		Twice daily dosing	
		KM rate (n/N)	HR (95% CI) ¹	KM rate (n/N)	HR (95% CI) ¹
5 mg	1.7% (4/252)	2.9% (2/77)	1.67 (0.31–9.14)	1.4% (1/77)	0.81 (0.09–7.23)
10 mg	1.7% (4/252)	7.6% (7/99)	4.74 (1.39–16.19)	5.5% (5/96)	3.40 (0.91–12.65)
20 mg	1.7% (4/252)	10.6% (8/78)	6.69 (2.01–22.21)	10.7% (8/79)	6.43 (1.94–21.37)

Stratum 1 – Concomitant ASA

TIMI Major Bleeding, TIMI Minor Bleeding, and Bleeding Requiring Medical Attention

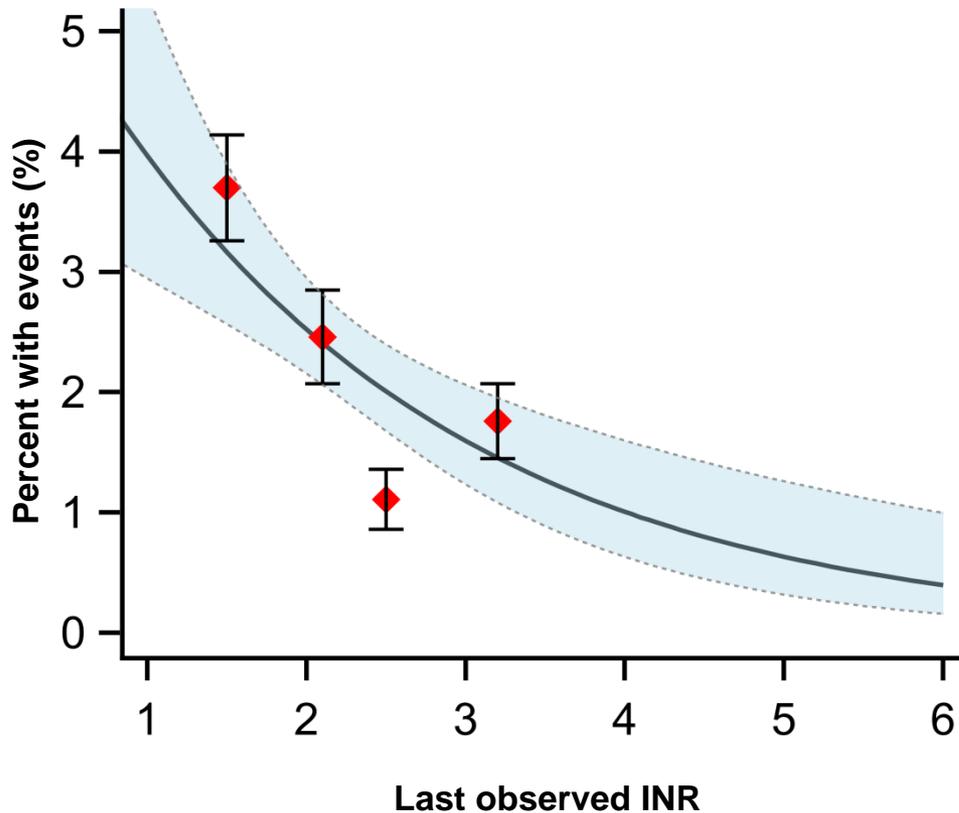
Effect on PT is Concentration Dependent



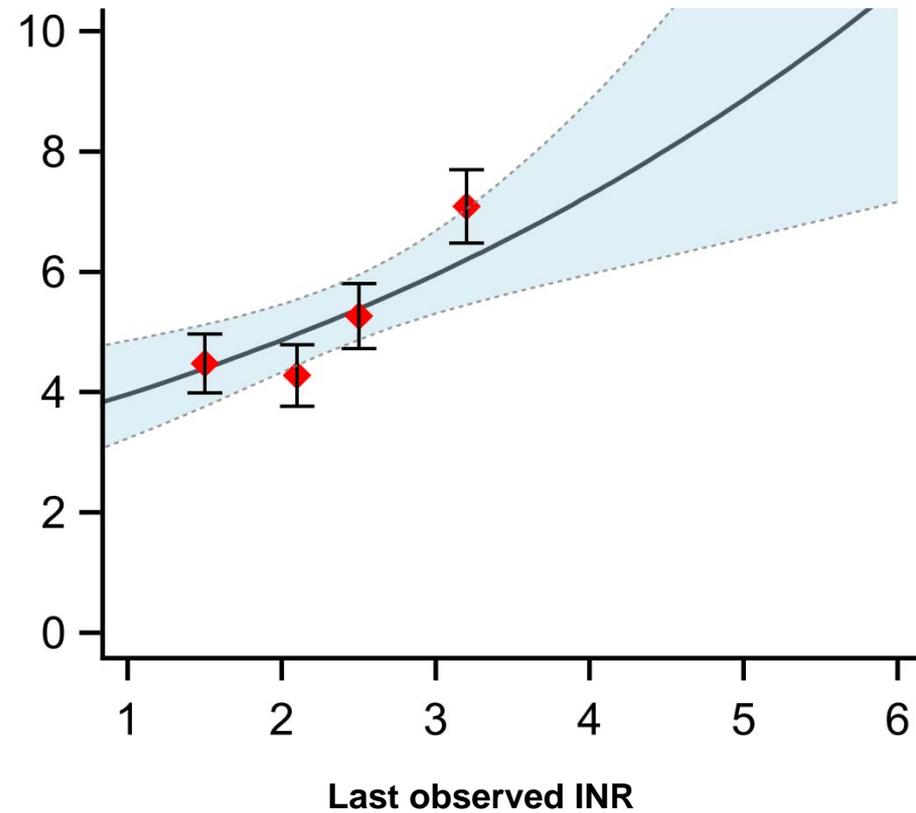
“The established close-to-linear PT/rivaroxaban plasma concentration relationship in Phase 2 supported the use of PT exposure-driven safety and efficacy analyses for the Phase 3 trials.”

ROCKET Warfarin – Expected Relationship between INR / Ischemic Stroke and INR / Major Bleeding

Ischemic Stroke

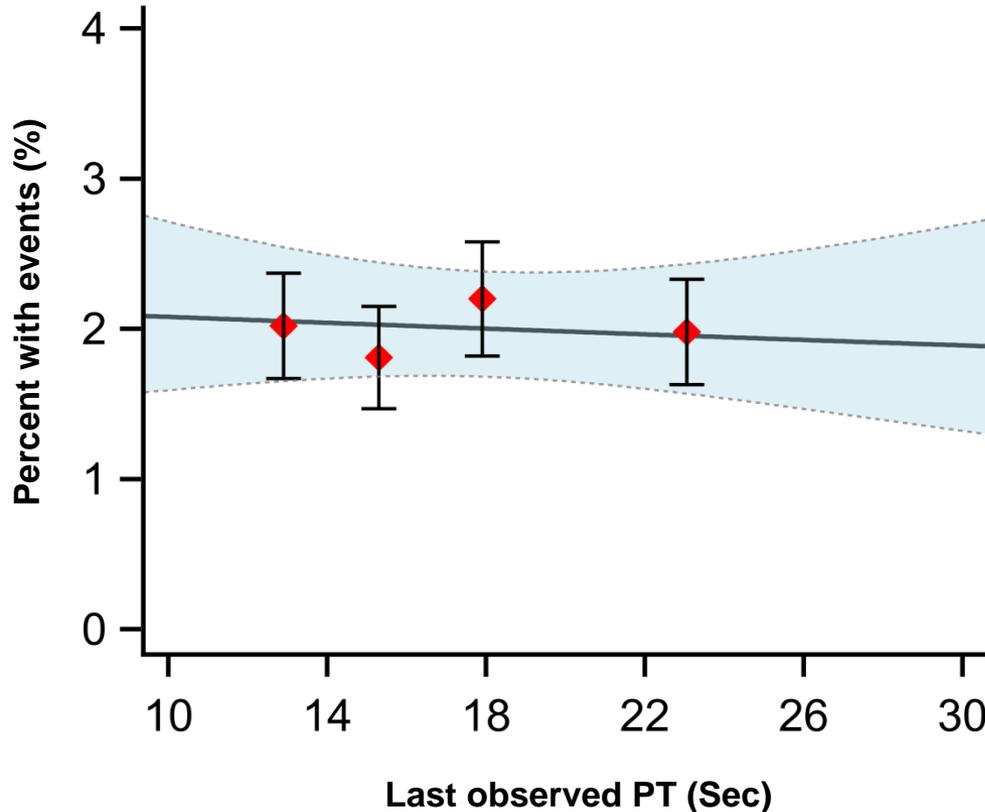


Major Bleeding

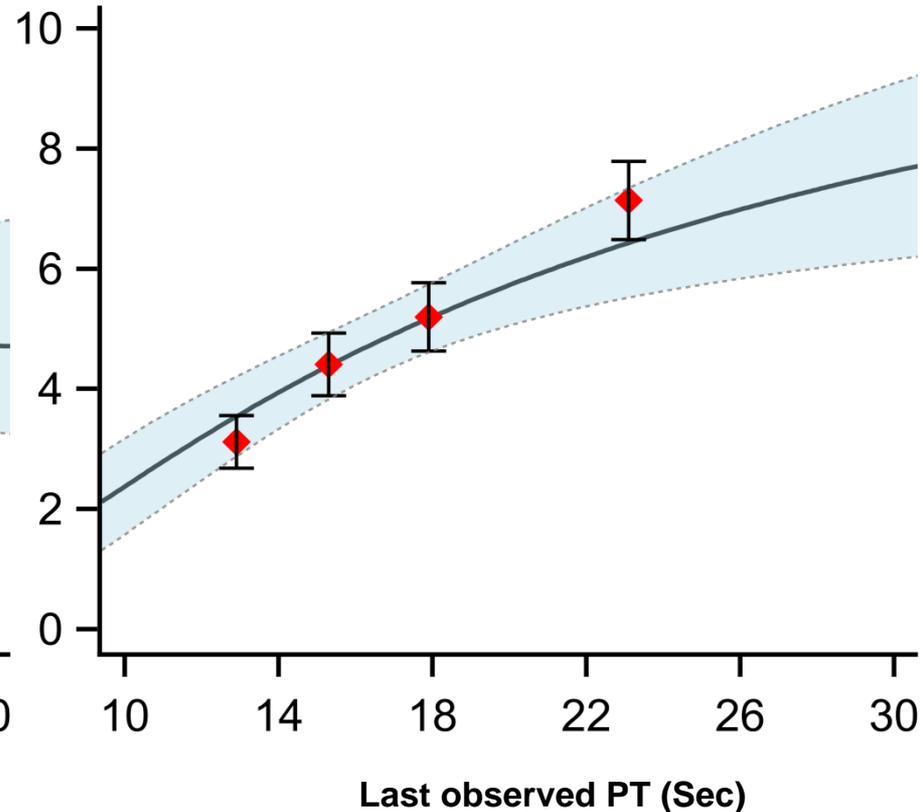


ROCKET Rivaroxaban – PT dependent increased Risk for Major Bleeding but No Relationship for Ischemic Stroke

Ischemic Stroke



Major Bleeding



Conclusions

- Clinical pharmacology attributes suggest BID dosing of Rivaroxaban
- VTE studies do not provide a firm basis for the dose and regimen studied in ROCKET
- 20 mg QD dose of Rivaroxaban in ROCKET
 - Twice the approved VTE prevention dose (10 mg QD)
 - Lower and split dosing incorporated into ATLAS ACS-2
 - 2.5 mg BID
 - 5.0 mg BID

Conclusions (continued)

- Ischemic Stroke and Major Bleeding in ROCKET
 - Warfarin: increasing INR associated with decreasing ischemic stroke and increasing major bleeds
 - Rivaroxaban: flat PT/ischemic stroke relationship, but increasing PT associated with increasing major bleeds