



Design of an adaptive phase II dose finding study for a novel FXa inhibitor

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Quantitative Solutions, Pfizer, and Pharsight

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Background

- ◆ PD 0348292 is an oral direct Factor Xa (FXa) inhibitor under development for prophylaxis and treatment of venous thromboembolism (VTE) and prevention of stroke in atrial fibrillation
- ◆ Only currently available oral anticoagulants are Vitamin K antagonists (e.g., warfarin), which have significant issues
- ◆ Phase 1 studies with PD 0348292 have demonstrated:
 - Proof of mechanism based on biomarker response
- ◆ Dose selection critical for any anticoagulant; consequences of underdosing (thrombosis) and overdosing (bleeding) are serious
- ◆ Goal for VTE prophylaxis: Find a dose equivalent to the current gold standard of enoxaparin 30 mg BID

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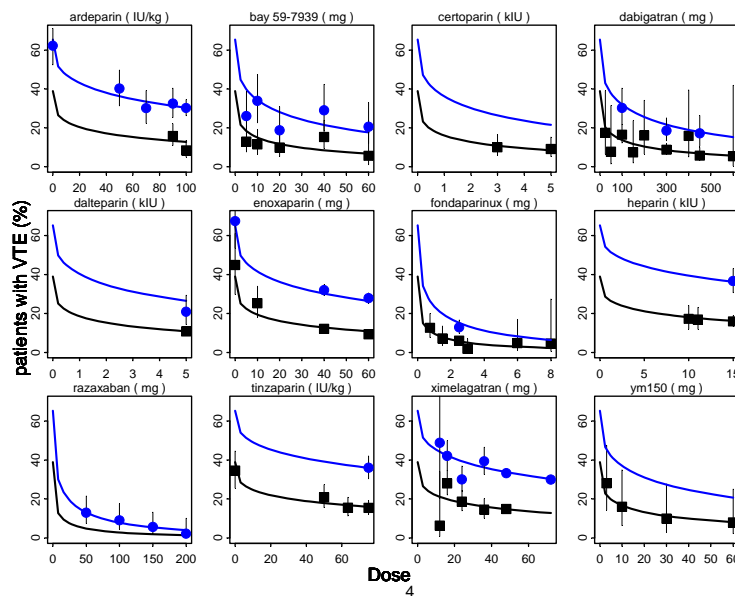
What do we know about dose response relationships for VTE prophylaxis?

- ◆ Data base for VTE prophylaxis
 - 21 compounds
 - 36,235 patients
 - VTE, proximal DVT, PE and bleeding endpoints
 - Hip and knee replacement
 - Patient characteristics and treatment characteristics
- ◆ Characterized dose response for VTE and bleeding

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Dose response relationship for VTE prophylaxis in hip (black) and knee (blue) surgery



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How can we improve dose finding?

- ◆ Strategy: can we use an in-vitro biomarker assay to predict PD 0348292 dose-response relationship for VTE and bleeding?
- ◆ Biomarker:
 - Inhibition of thrombin generation for PD 0348292 and comparator anticoagulants (LMWH, direct and indirect FXa inhibitors, direct thrombin inhibitors)
- ◆ Model:
 - Linked biomarker response and clinical outcome for comparators with an integrated PK/PD model
 - Estimated ratio between bio-marker potency and potency for VTE and bleeding

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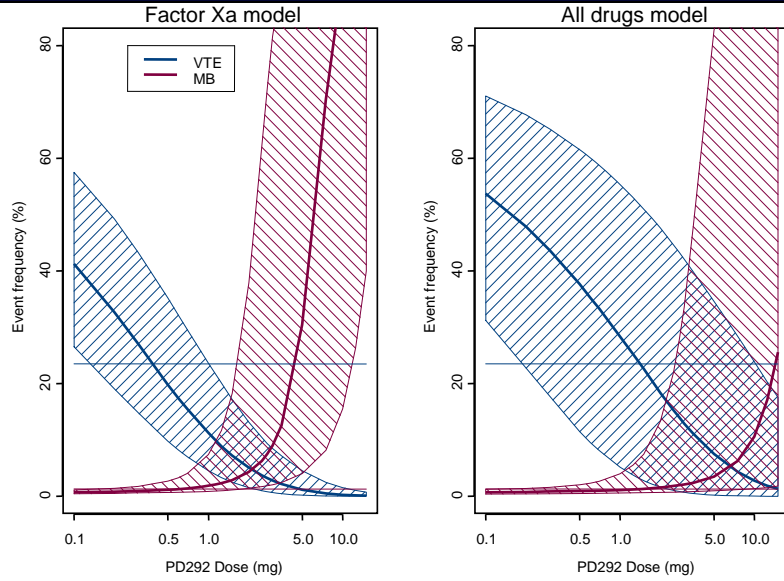
Prediction of PD 0348292 Dose Range Equivalent to Enoxaparin 30 mg BID [80% CI]

- ◆ 5 compounds used in biomarker-scaling model:
 - Ximelagatran, enoxaparin, dalteparin, fondaparinux, and razaxaban
- ◆ No consistent biomarker scaling found among 5 compounds
 - all drugs model (ADM)
 - Large uncertainty in dose response
 - Dose equivalent VTE: 1.4 mg [0.24 to 8.6 mg]
 - Dose equivalent bleeding: 1.6 mg [0.35 to 7.6 mg]
- ◆ Consistent scaling found for FXa inhibitors razaxaban and fondaparinux
 - FXa model
 - Dose equivalent VTE: 0.38 mg [0.22 to 0.67 mg]
 - Dose equivalent bleeding: 0.6 mg [0.24 to 1.5 mg]

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Predicted PD 0348292 VTE and MB Dose-Response



Horizontal lines: event rates for enoxaparin 30 mg BID

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Design of Phase 2B Study

Objectives of Phase 2B VTE Prophylaxis Study

- ◆ Estimate the dose of PD 0348292 that is equivalent to enoxaparin 30 mg BID for VTE in total knee replacement
 - Desire high probability ($\geq 80\%$) that both VTE & MB rates for PD 0348292 are similar (≤ 1.3) to enoxaparin 30 mg BID
 - Characterize the dose-response of PD 0348292 for VTE and MB
 - Select 1 dose for phase III; interpolated dose is OK.
- ◆ Protect subjects from excessive VTE and MB
- ◆ Select a design that performs well given current uncertainty in dose response

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Recommended Design: Adaptive Dose Range

- ◆ 6-arm parallel group with adaptive dose range based on interim analyses of VTE and MB
 - Start with 5 initial doses of PD 0348292 (0.1 to 2.5 mg QD)
 - Prune PD 0348292 doses based on excessive VTE or MB
 - Add higher PD 0348292 doses (4 and 10 mg QD) if prune lower doses or MB rate acceptable
 - Include 30 mg BID Enoxaparin as control
- ◆ Fixed total sample size of 490 evaluable subjects (833 total subjects due to 40% unevaluable rate)
 - Allocate 2:1 for Enoxaparin
 - 70/arm
- ◆ Interim analyses after every 70 evaluable subjects (a total of 6)

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Clinical Trial Simulation Facilitated Evaluation of Many Designs

- ◆ Using the VTE and MB dose-response models for PD 0348292, simulated the outcome of each trial design 1000 times
- ◆ Assessed trial performance using various metrics;
 - Primarily the power to find a dose equivalent to enoxaparin
 - But also the number of bleeds and VTEs (especially proximal and PE)
 - And numerous others; conditional power, likelihood to prune/add, sample size/group
- ◆ Evaluated sensitivity to sample size, doses, adaptive modifications (pruning and adding doses), dose selection criteria, dose response model structure

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What is a good initial dose range?

Table 2. Predicted VTE and MB Incidence (Median [25th, 75th Percentile]) for Proposed PD 0348292 Doses

Dose (mg)	FXa Model		All Drugs Model	
	Predicted VTE Incidence (%)	Predicted MB Incidence (%)	Predicted VTE Incidence (%)	Predicted MB Incidence (%)
0.1	41 (33, 50)	0.70 (0.55, 0.90)	54 (42, 63)	0.68 (0.51, 0.92)
0.3	27 (20, 35)	0.92 (0.70, 1.3)	44 (30, 56)	0.81 (0.59, 1.1)
0.5	20 (14, 27)	1.2 (0.84, 1.7)	38 (23, 51)	0.90 (0.64, 1.3)
1.0	11 (7, 17)	1.9 (1.2, 3.4)	28 (14, 43)	1.1 (0.76, 1.8)
2.5	3.7 (1.9, 6.5)	6.2 (2.8, 20)	15 (5, 30)	1.8 (1.0, 4.7)
4.0*	1.8 (0.84, 3.6)	19 (6.1, 58)	9.9 (2.5, 24)	2.7 (1.3, 11)
10.0*	0.24 (0.071, 0.68)	92 (46, 100)	2.8 (0.32, 11)	11 (2.7, 73)

* Doses would only be studied if dose-decision analyses estimated acceptable incidence of major bleeding.

- ◆ Initial doses: 0.1, 0.3, 0.5, 1, 2.5 mg QD
 - Safe under both models
 - P(eq. dose < 2.5)=1 under FXa model and 0.65 under ADM model
- ◆ Explore 4 and 10 mg QD if it is safe and necessary to do
 - Joint P(eq. dose <10)>0.95

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Probability that VTE and MB rates <= 1.3 for PD292 doses

PD 292 Dose	FXa model	all drugs model
0.1 mg	6.1	5.9
0.2 mg	41	14
0.3 mg	68	20
0.5 mg	77	27
1 mg	43	32
2.5 mg	6.2	27
5 mg	0.7	19
7.5 mg	0.1	13

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How do we evaluate trial performance?

- ◆ Metric for evaluation:

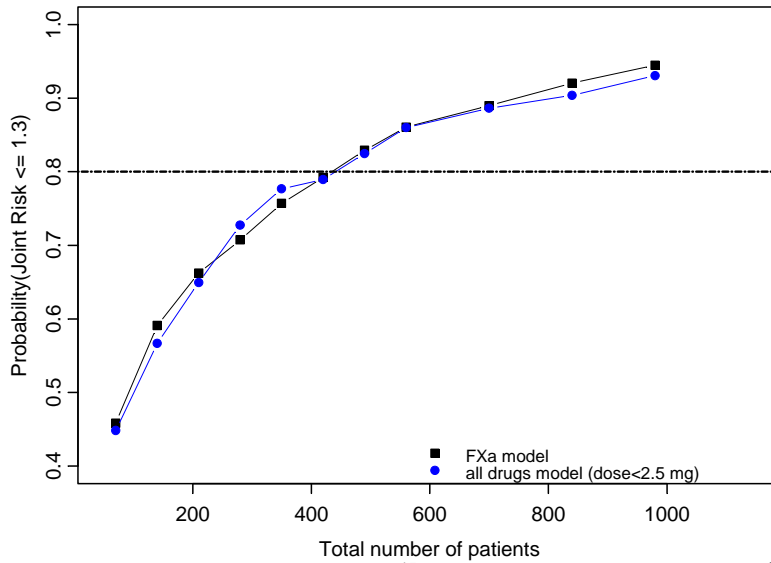
$$Joint_{risk} = \max\left(\frac{VTE_{PD292, D_{eq, est}}}{VTE_{Enox}}, \frac{Bleed_{PD292, D_{eq, est}}}{Bleed_{Enox}}\right)$$

- ◆ Calculate equivalent dose of PD 292 to Enoxaparin on basis of phase II VTE results ($D_{eq, est}$)
- ◆ Calculate true VTE and bleeding rate for selected dose ($VTE_{PD292, D_{eq, est}}$) on basis of simulation model
- ◆ Compare these rates to the true VTE and bleeding rates for Enoxaparin (VTE_{Enox})
- ◆ Calculate the maximum ratio
- ◆ Determine how often out of 1000 replicates of a particular trial design the maximum ratio falls below a certain threshold value
 - 1.3 was selected as equivalence value

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What sample size should we consider?



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Probability to detect a dose equivalent to Enoxaparin

Power as a function of sample size and equivalent dose range

N (total)	power to achieve equivalence of 1.3		80% chance equivalence is at least
	0.1 to 2.5 (mg)	2.5 to 10 (mg)	0.1 to 10 mg
490 (820)	0.83	0.80	1.28
735 (1225)	0.91	0.86	1.22
980 (1633)	0.94	0.86	1.18

Another major factor on power is whether we select 1 or 2 doses for Phase III

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What is the value of a model-based dose response analysis vs. pair-wise comparisons?

Efficiency is how many times larger the sample size would have to be using a pair-wise comparison in order to have a standard error as small as that obtained from an integrated dose response model.

- For example, at the 1.0 mg dose, you'd need 197 (=2.81 x 70) subjects to have the same as precision as that with 70 subjects in a model-based analysis.

Dose (mg)	N per dose	p DVT	SE (p DVT) Individual	SE (p DVT) Integrated	Efficiency *
0.1	70	0.410	0.0588	0.0490	1.44
0.3	70	0.262	0.0526	0.0276	3.62
0.5	70	0.190	0.0469	0.0234	4.01
1.0	70	0.104	0.0365	0.0218	2.81
2.5	70	0.0326	0.0212	0.0138	2.35

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Importance of active control?

◆ Why Enoxaparin as active control?

- Previous trials have shown a large degree of between trial variability in the VTE frequency for Enoxaparin 24% [14 to 37%; 80% CI]

◆ Why “doubling up” on Enoxaparin sample size?

- Doubling up reduces the total sample size by about 35%

◆ Value of Bayesian analysis that includes prior?

- Performance of Bayesian analysis with equal group allocation is about the same as proposed design
- Value of Bayesian analysis is low due to large trial-to-trial variability in Enoxaparin effect and large uncertainty in dose response of PD292

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How do we add or prune doses?

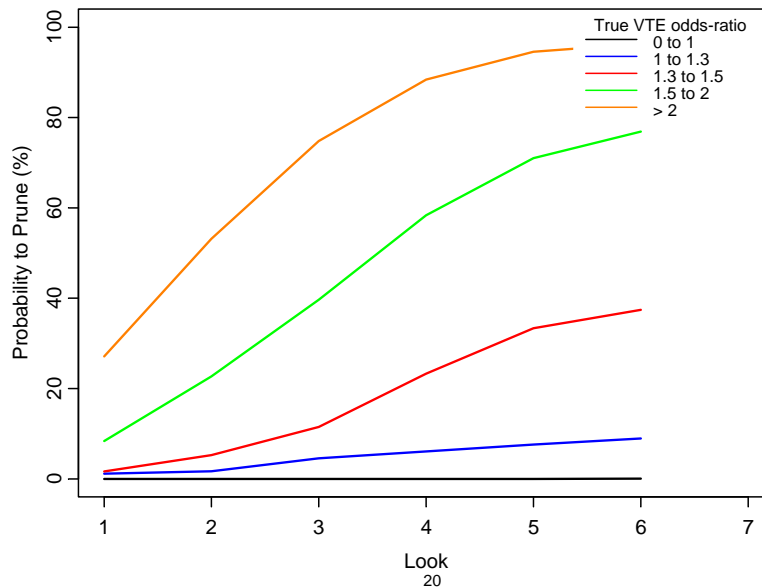
- ◆ **Pruning for VTE:**
 - prune lowest dose if 1-sided 90% LCB* of estimated odds-ratio > 1.5**
- ◆ **Pruning for MB:**
 - prune all doses having 1-sided 90% LCB* of estimated MB rate > 5%
- ◆ **Add 4 or 10 mg of PD292**
 - add next highest dose if the smallest dose was pruned for VTE and the point estimate of the bleeding frequency at the next highest dose is less than 5%
 - Add the next highest dose if 1-sided 90% UCB* of estimated MB rate of the highest dose currently in the trial < 5%.
 - Maintain a maximum of 5 active treatment arms. If 4 mg is added, 0.1 mg is pruned, and if 10 mg is added, 0.3 mg is pruned.
- ◆ **An extra safety valve**
 - the first look can be triggered early before 70 evaluable patients are available if the cumulative number of bleeds in any arm is 5 or more.

* LCB = lower confidence bound
 ** (PD 0348292 dose vs. enoxaparin)

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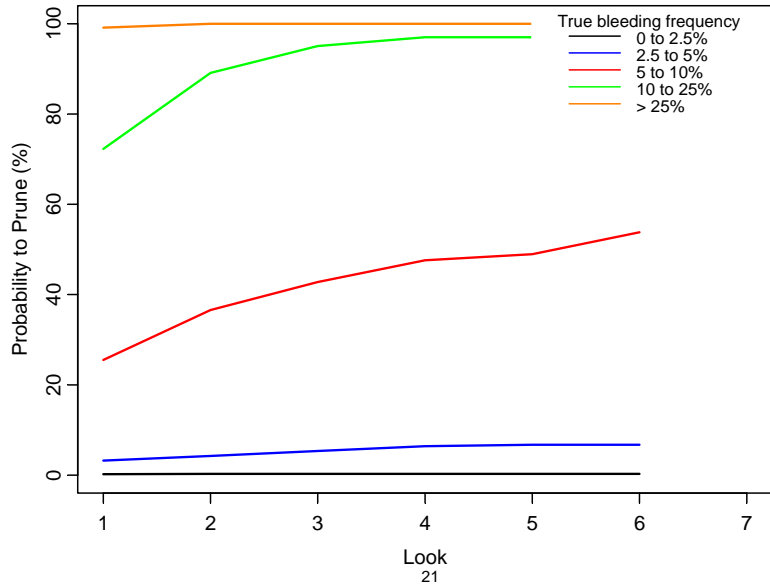
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What is the chance that we prune the wrong/correct dose for VTE?



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What is the chance that we prune the wrong/correct dose for bleeding?



Probabilities to Prune or Add an Arm; Overall and Conditional on the "True" Equivalent Dose (All Drugs Model)

action	true equivalent dose (mg)								
	all	<0.1	0.1-0.3	0.3-0.5	0.5-1	1-2.5	2.5-4	4-10	>10
prune 0.1	85	0	35	77	92	98	98	98	98
prune 0.3	65	19	3.7	11	44	89	97	96	97
prune 0.5	52	37	10	2.1	15	66	84	94	96
prune 1	40	78	25	9.4	6	21	62	86	93
prune 2.5	37	93	73	49	22	11	11	44	89
add 4	66	0	4.6	29	57	80	93	95	96
add 10	42	0	0.92	5.2	14	44	76	79	92

What sample size do we expect per dose?

	all drugs model	
	overall	pruned/ added
Enox 60 mg	140	
0.1 mg	29	19
0.3 mg	48	29
0.5 mg	62	39
1 mg	71	46
2.5 mg	69	32
4 mg	43	63
10 mg	23	52

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Pruning keeps incidence rates in acceptable range

Table 4. Expected Overall Incidence of Efficacy and Safety Events [with an Adaptive Design]

Endpoint Incidence (%)	FXa Model		All Drugs Model	
	PD 0348292	Enoxaparin	PD 0348292	Enoxaparin
MB	2.1	1.4	1.6	1.4
VTE	22.5	28.6	31.0	29.5
PE and/or Proximal DVT	4.0	5.2	5.5	5.2

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Overall the pruning criteria work well

- ◆ There is about a 5% cumulative chance that a dose that meets the equivalence criteria is pruned
- ◆ There is about a 70% cumulative chance that a dose that does not meet the equivalence criteria is pruned
- ◆ Pruning does not drastically change the power of the trial
- ◆ Pruning keeps the expected total number of bleeds to less than 12 (max=5/arm) and total number of Prox VTE + PE to less than 30 (max=11/arm)
- ◆ There is a 92% chance to add the 4 mg dose if the “true” equivalent dose is greater than 2.5 mg

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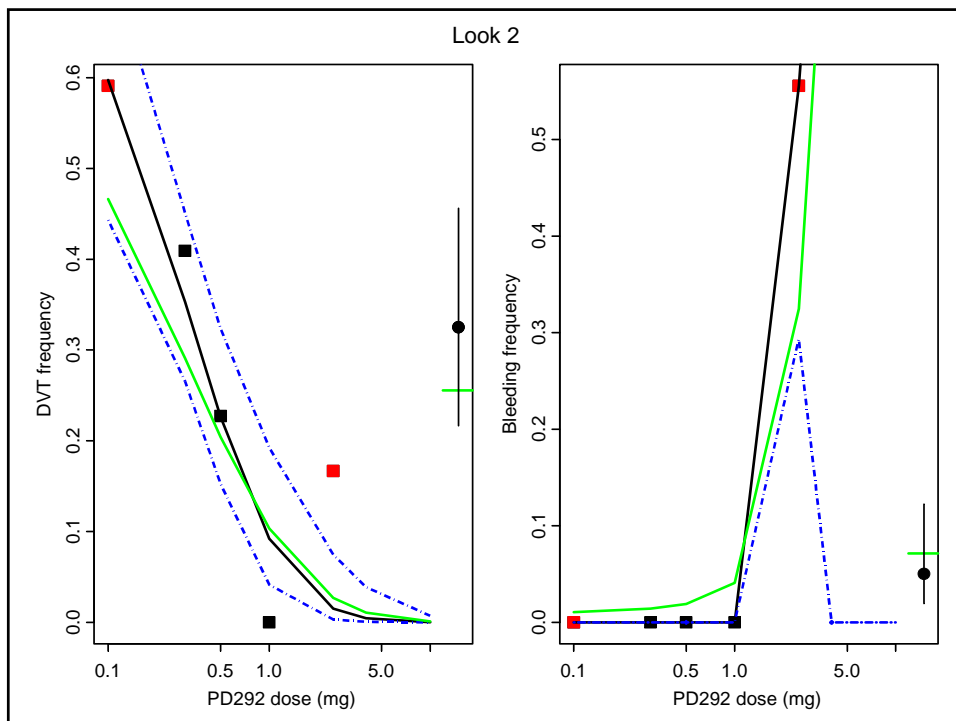
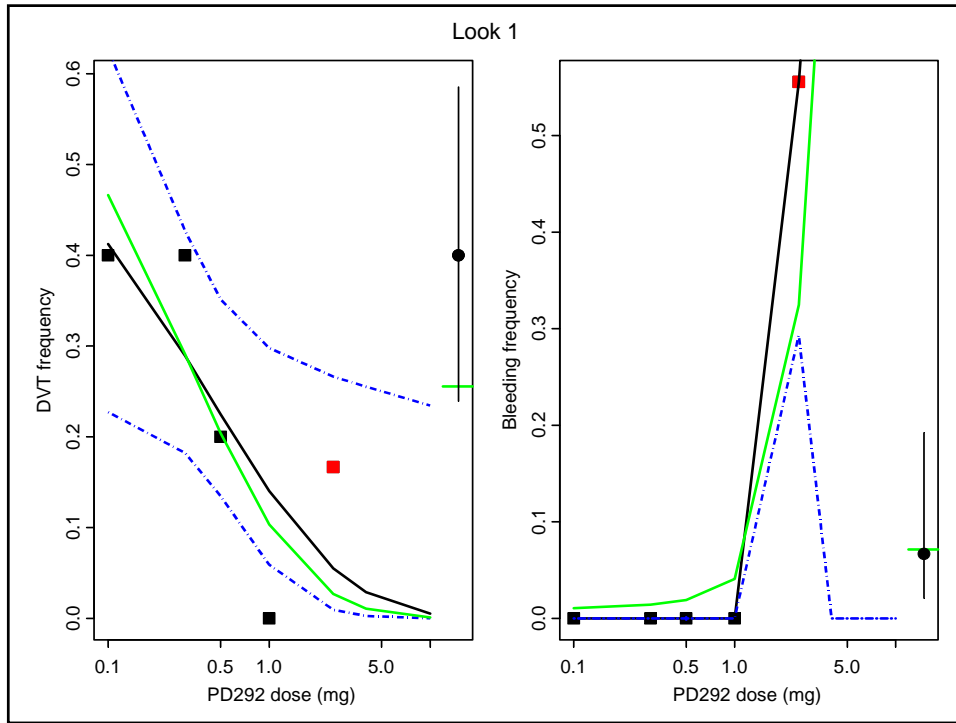
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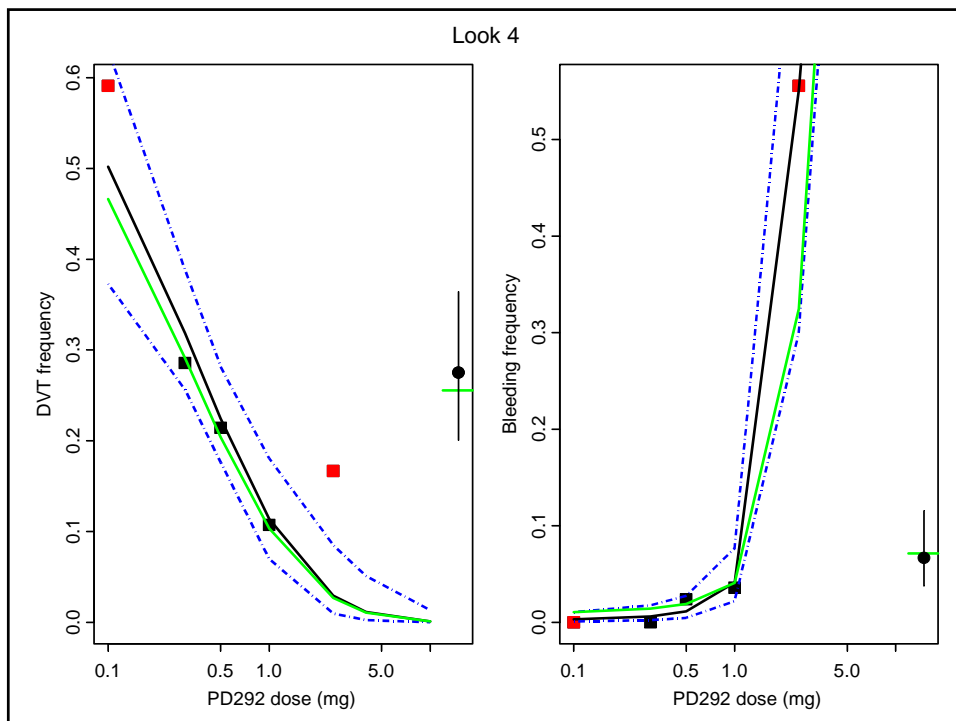
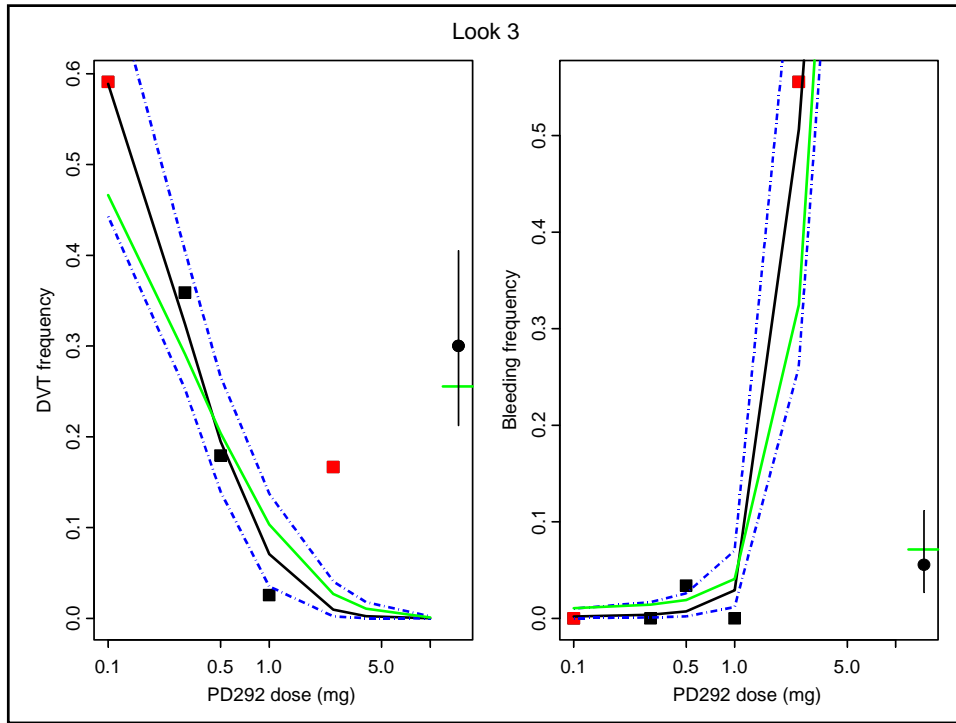
Example

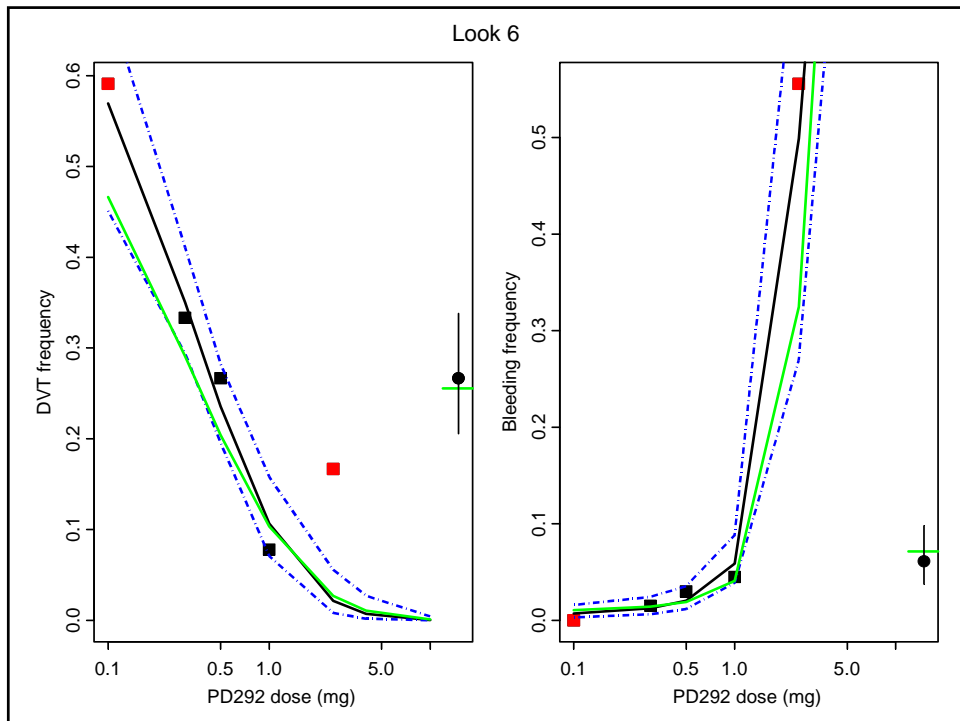
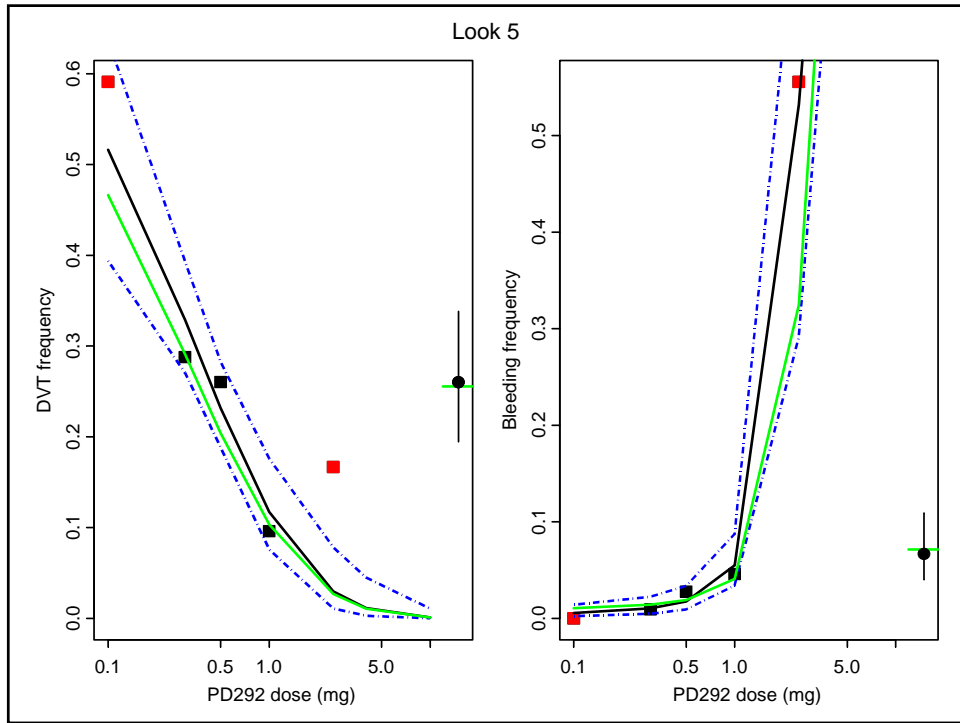
- ◆ 2nd replicate for original design
 - Start with 0.1, 0.3, 0.5, 1, 2.5
 - Target N=490; 70/arm PD292, 140/arm Enox
 - 6 looks; every 70 patients
 - FXa model
- ◆ This example shows how we prune a high dose for excessive bleeding at the first look and a low dose for excessive VTE at the 2nd look
- ◆ Black symbols are estimated frequencies
 - Enox is on the far right
 - If symbol turns red, that dose is pruned
- ◆ Black line is estimated dose response
 - Blue dashed line is 90% confidence interval
- ◆ Green line is “true” dose response relationship

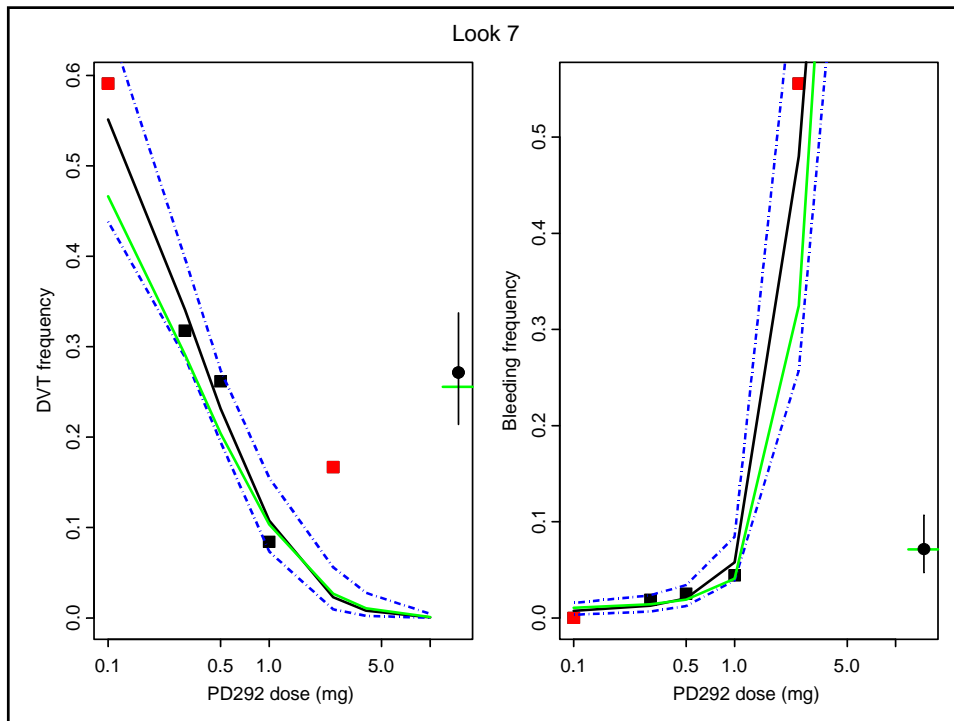
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What were the major discussion points upon management review

- ◆ When should we perform the first interim analysis?
- ◆ How many patients are enough to reach a firm conclusion?
- ◆ Argument for Earlier: remove dose groups that are really bad and minimize patient exposure to these doses
- ◆ Argument for Later: reduce chance of making wrong decision. There is site variability in VTE and Bleeding rates, which would increase chance of making wrong decision at small sample size and potential imbalance between treatment groups across sites

Modifications to Initial Design

	Original Design; 6 Total Dose Analyses (N=833)	Delay First Analysis; 4 Total Dose Analyses (N=833)	Delay First Analysis/ ↑ Sample Size (N=1,250)	No Delay/ ↓ Sample Size (N=1,250)	1 st Dose Analysis @ 21/Arm Eval (35 Rand); 5 Total Dose Analyses (N=1,225)	1 st Dose Analysis @ 21/Arm Eval (35 Rand); 4 Total Dose Analyses (N=1,225)
Overall likelihood of identifying the "right" P3 dose	82%	83%	87%	90%	89%	89%
Likelihood of identifying the "right" P3 dose (0.1 – 2.5 mg)	83%	86%	90%	91%	91%	90%
Likelihood of identifying the "right" P3 dose (2.5 – 10 mg)	80%	75%	81%	87%	86%	86%
Cumulative likelihood of wrongly pruning the "right" P3 dose	5.6%	3.2%	3.7%	5.4%	4.6%	4.4%
Likelihood of First Look wrongly pruning the "right" P3 dose	1.4%	0.3%	0.4%	0.7%	0.5%	0.5%
No. of VTEs (approx.)	100	110	165	150	151	156
No. of MBs (approx.)	10	10	15	15	16.2	15.9
					Dose analysis increment 15/arm eval (25 rand)	Dose analysis increment 21/arm eval (35 rand)
			35		Trigger for early dose analysis: 6/35 MB, 7/21 pDVT+PE. Prob(MB trigger)=13%, Prob (pDVT+PE trigger)=10%	

Some further thoughts on power calculations

- ◆ Dose selection is done on basis of equivalence with VTE
- ◆ Trial performance is judged on basis of VTE and bleeding
- ◆ Careful evaluation of prior shows there is some chance that there isn't a dose that can satisfy both criteria
- ◆ This chance is dependent on the magnitude of the equivalent dose and prior model
 - 0% for FXa model and around 10% for all drugs model

Some further thoughts on power calculations

Look (N)	FXa model		All drugs model	
	VTE	bleeding	VTE	bleeding
1 (130)	0.82	0.88	0.77	0.72
2 (280)	0.89	0.95	0.88	0.77
3 (425)	0.92	0.98	0.91	0.79
4 (570)	0.95	0.99	0.94	0.83
Final (735)	0.96	0.99	0.96	0.86

- ◆ Table list probability to find equivalent dose for VTE or Bleeding

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Conclusions

- ◆ The trial finished this summer and performed well
- ◆ Doses were pruned and added
- ◆ The equivalent dose was selected with high precision
- ◆ Additional trials will have to show whether the selected dose performs as expected

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