

# Designing Adaptive Ph2-Ph3 programs for Neuropathic Pain

Nitin Patel & Jim Bolognese

Cytel, Inc.

# Neuropathic Pain Application Subteam of the PhRMA/DIA Adaptive Programs Network

- Keaven Anderson, Arnold Gammaitoni, David Hewitt, Merck
- Zoran Antonijevic, Quintiles
- Jim Bolognese, Cytel
- Christy Chuang-Stein, Pfizer
- Frank Miller, Astra Zeneca
- Nitin Patel, Cytel (lead)
- Jose Pinheiro, J&J

# Outline

- Overview of Simulation Plan
- Describe first stage of plan (completed)
  - Ph2b and Ph3 designs
  - Commercial model for Net Present Value (NPV)
  - Dose Response Scenarios
- Simulation Results
- Concluding Remarks

# Simulation Plan Overview

- Investigate impact of Ph2 sample sizes, number of doses and adaptive designs on a PH2b+Ph3 development program for Neuropathic Pain
- Outcome assessed *at program level* by number of patients required, probability of success (PoS) and profit
  - PoS measured by probability of 2 pivotal Phase 3 trials demonstrating statistically significant drug effect compared to placebo with difference in mean response at least equal to “delta.”
  - Profit measured by E(NPV). NPV determined by relationship of efficacy and tolerability profile demonstrated by Ph3 trials to typical profits of comparator drugs and trial costs.

# Efficacy and Safety Response

- 0-10 pain scale used to measure efficacy for treatment of neuropathic pain in both Ph2 (12 wks.) and Ph3 (12 months)
  - Target level of response (delta) is mean difference from placebo of 1 unit
  - SD of response known to be 2 units in Ph2 and Ph3
  - Mean Dose Response is 4-Parameter Logistic (4PL) function
- Two types of AE' s:
  - 'nuisance' AE' s that are non-transient and not manageable by other means (e.g. weight gain, sexual function AE' s)
  - serious AE' s with rare probability of occurrence and only likely to be detected in the post marketing stage (e.g. CV events, liver failure. simulate the risk of stopping the program if an important numeric increment of this serious AE is observed.

# Nuisance AE' s

- Moderate probability of occurrence (e.g., 0.2 or 0.3 maximum binomial probability).
  - will not cause stoppage of development or drug approval, but will lower the benefit/risk profile and negatively impact sales.
  - Placebo rate for nuisance AE' s= 0.15.
  - drug rate 0.2-0.3 assumed similar to marketed products (>0.3 worse; <0.2 better)
- *In first stage of work reported here, we rely on selection of lowest dose meeting target to reflect monotone increase in rate of nuisance AE' s with dose. Subsequently we will simulate nuisance AE rates during Ph 2b trials and use them in selecting dose(s) to carry forward to Ph3*

# Ph2b and PH 3 Designs

In first stage of work we consider traditional fixed designs with equal allocation to all arms for Ph2b and Ph3 designs

- Ph2 prior chosen to be practically flat over likely range of parameters of 4PL dose response
- For each Ph2b trial replicated MCMC samples from posterior distribution are used to estimate mean response at each dose and placebo:
  - If no dose meets target diff from pbo, no Ph3 trials are conducted
  - If at least one dose meets target select smallest dose,  $d_i$ , that meets target to run two concurrent Ph 3 trials each with sample size for 95% power ( $\alpha=0.025$ , 1-sided)

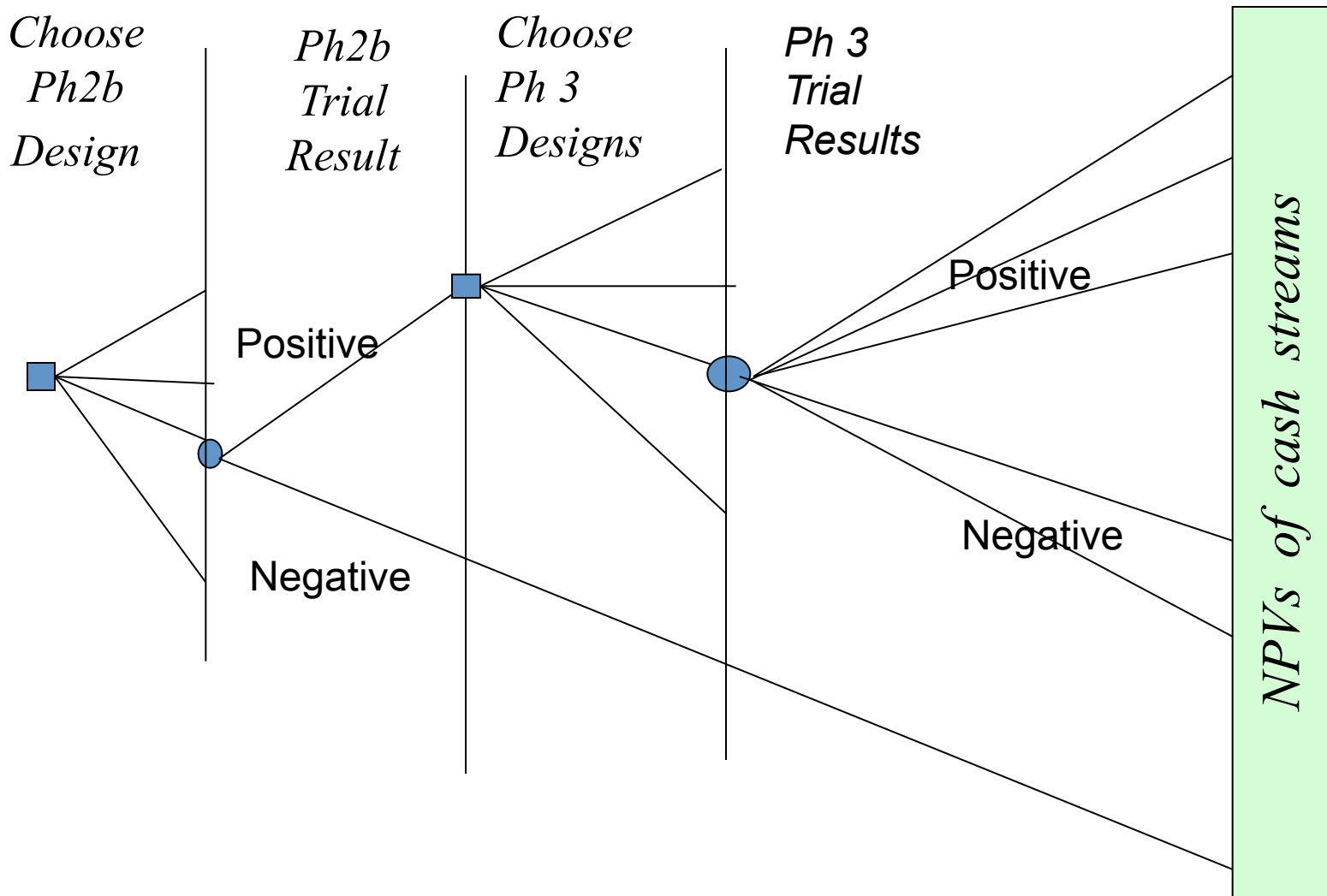
# ICH E1A guidance for minimum number of subjects for dose approval

- ICH E1A guidance applicable for neuropathic pain (among others) is to have 1500 patients treated at the target dose of interest, with at least 500 treated for at least 6 months and at least 100 for at least 1 year. These minimum sample size requirements are for the 3 combined Ph2 and Ph3 trials along with other unblinded studies.
- We assume that Ph2 subjects on study drug are switched to the Ph3 dose and pbo subjects are continued on pbo for the Ph 3 treatment period of 12 months for safety assessment.
- We adjust Ph 3 sample sizes to follow this regulatory guidance assuming no other studies will be conducted. **In every case we have considered this adjustment results in Ph3 being over-powered for efficacy.**

# Calculating PoS and ENPV

- For Ph2b trial replicates where a dose was selected to carry into Ph3 trials:
  - Calculate predictive PoS =  $\Pr(\text{Both Ph3 trials show significance}) = \Pr(\text{Technical Success}) = \Pr(\text{TS})$  using Ph2b posterior distribution.
  - Use this probability to combine:
    - NPV|TS calculated from Commercial model
    - Negative NPV resulting from Ph2b and Ph3 trial costs when there is no Technical Success
- Estimate  $E(\text{NPV})$  by averaging across simulations. Also compute empirical probability distribution of NPV to show risk.

# Decision Analysis Tree



# Commercial Model

- Let  $e^*(d_i)$  denote the true mean difference in efficacy from placebo for dose  $d_i$ . Let  $s^*(d_i)$  denote the nuisance AE rate for dose  $d_i$
- These values determine the fifth year revenue (net of variable costs) from marketing a dose by interpolation in the table below. This table was constructed based on discussions with David Hewitt, MD, and Arnold Gammaitoni, MD, clinical development experts in the neuropathic pain therapeutic area.

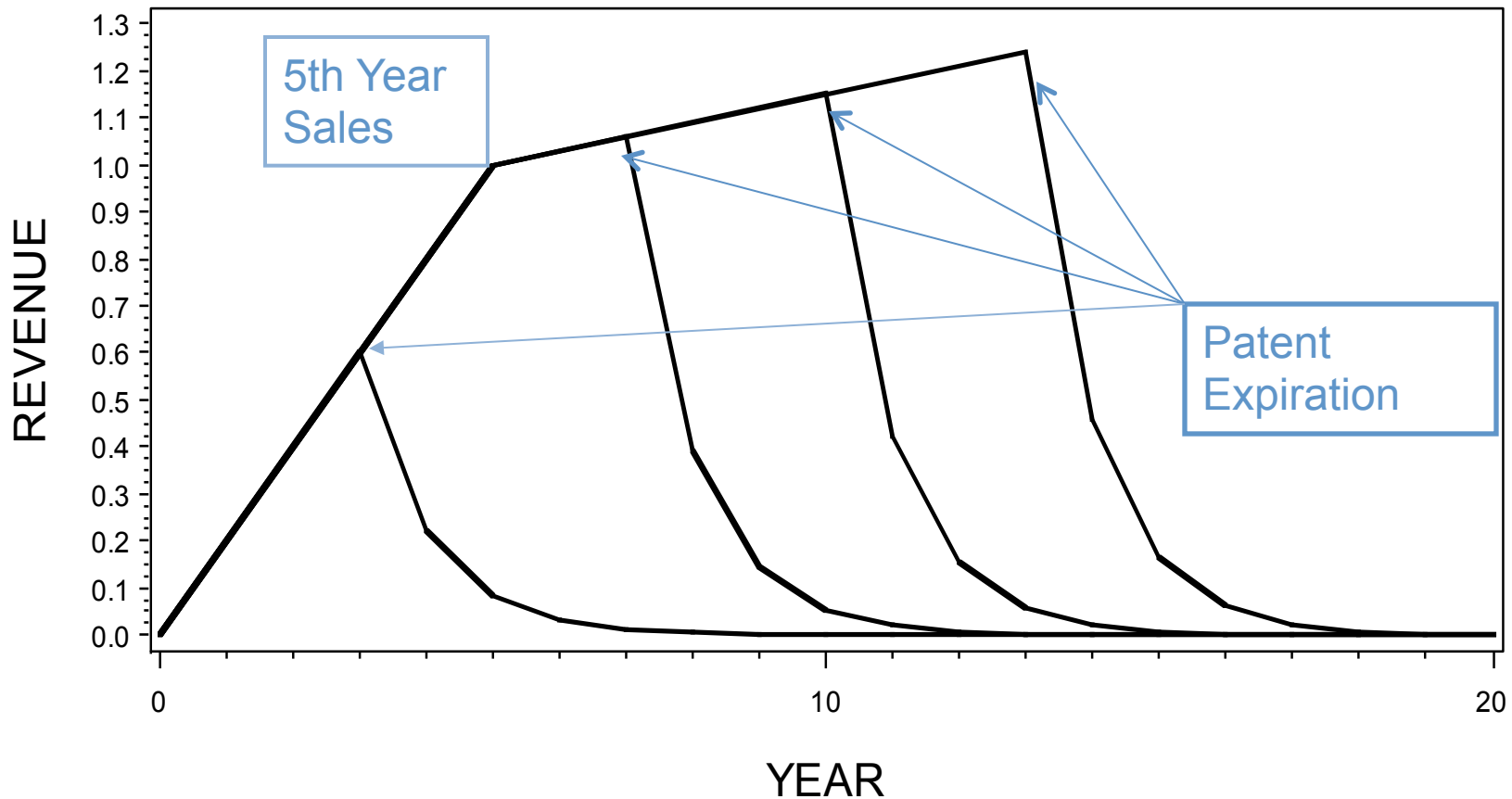
5th year sales(\$B)

$e^*(d_i)/s^*(d_i)$	0	0.1	0.25	0.4	0.75	1
0	0	0	0	0	0	0
0.4	0	0	0	0	0	0
0.9	1	1	0.75	0.25	0	0
1.25	1.5	1.5	1	0.5	0	0
1.75	2	2	1.5	1	0.25	0.25
2	2	2	1.5	1	0.25	0.25

# Time Profile of Net Revenue

Slope after 5<sup>th</sup> year =  $b$ , Decay parameter for period after patent expiration =  $c$

**Revenue over time for Effective Patent Life TP=3,7,10,13**  
( $S5=\$1B$ ,  $b=0.03$ ,  $c=1$ )



# Example

## Efficacy and Safety Dose Response

DRCurve	D0	D1	D2	D3	D4	D5	D6	D7	D8
Efficacy	0.000	0.001	0.034	0.217	0.567	0.854	1.002	1.068	1.099
Rate for Nuisance AE's	0.1	0.1	0.1	0.1	0.15	0.20	0.25	0.30	0.35

Base Case:

Ph2 Sample Size =  $30 \times 9 = 270$  subjects

# Parameter settings for Example

Ph3 alpha(1-sided)	0.025	Months of PH2b trial duration	
PH2_SD	2	per patient	3
PH3_SD	2	Months of PH3 trial duration	
Power	0.95	per patient	12
Target Multiplier	1	Lag between end PH2b trial	
Target Value	1	and start PH3 trial (months)	6
Duration of Dev. Time		Cost of manufacturing gear-up	\$1M
before the Ph2b trial (yrs)	2	Revenue model parameter b	0.1
Cost per site	\$15K	Revenue model parameter c	0.5
Cost per patient	\$3.5K	Discount rate per year	0.10
Patient Accrual per month		Total patent life (yrs)	17
per site in PH2b trial	0.5	Duration between end PH3	
Patient Accrual per mo.		trial and launch (months)	12
per site in PH3 trial	1	% of PH2 N completing long-	
# Sites in PH2b trial	50	term extension	50
# Sites in each PH3 trial	80	Minimum Subjects Required	
		for Safety on Selected Dose	1500

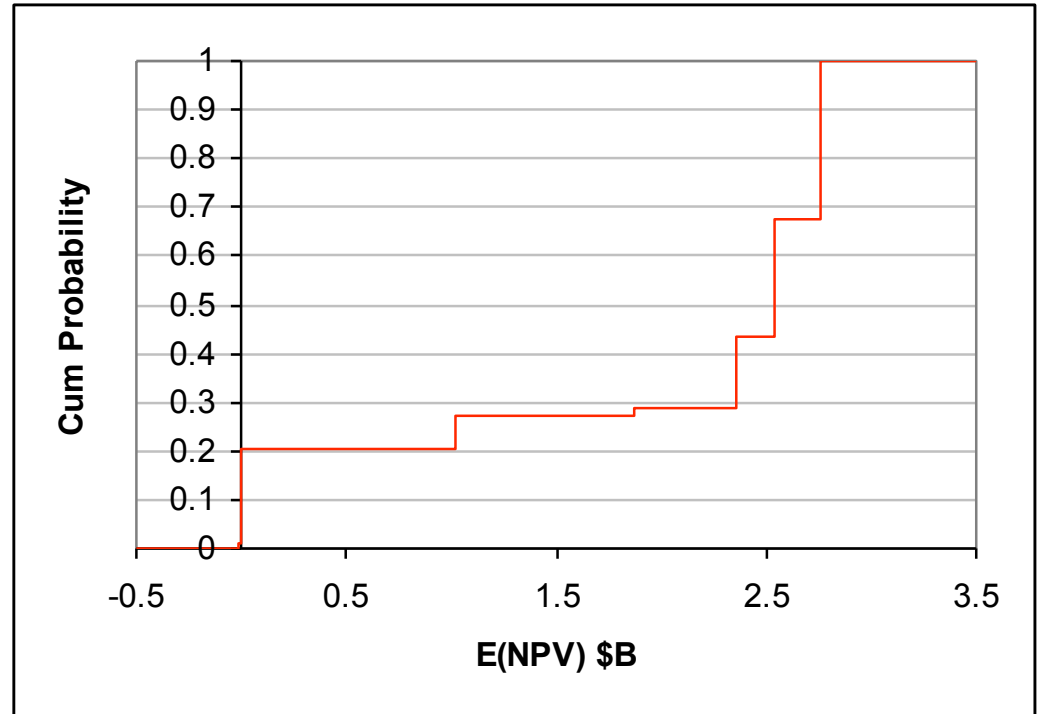
# Base Case

di	Probability di selected	Ph2Post_MEAN(di)	Ph2Post_MEAN(pbo)	Ph2Post_StDev(di)	Ph2Post_StDev(pbo)	SS_per_PH3trial	PH2_DUR(yrs)	PH3_DUR(yrs)	TOT_DEV_TIME(yrs) if Tech Succ	ExpectedNPV(\$B)
3	0.010	0.5196	-0.429	0.22	0.265	1380	1.15	2.44	7.09	-0.011
4	0.068	0.6292	-0.331	0.19	0.252	1380	1.15	2.44	7.09	1.021
5	0.244	0.7738	-0.197	0.18	0.234	1380	1.15	2.44	7.09	2.541
6	0.322	0.9198	-0.042	0.17	0.225	1380	1.15	2.44	7.09	2.764
7	0.146	0.9806	0.029	0.20	0.212	1380	1.15	2.44	7.09	2.362
8	0.014	1.1208	0.147	0.25	0.213	1380	1.15	2.44	7.09	1.873
.	0.196						1.15	.		-0.002

# Distribution of NPV

NPV(\$B)	PROB	CUM_PROB
-0.012	0.003	0.003
-0.011	0.007	0.010
-0.002	0.196	0.206
1.021	0.068	0.274
1.873	0.014	0.288
2.361	0.146	0.434
2.541	0.244	0.678
2.764	0.322	1.000

$E(NPV) = \$1.95B$



If hurdle value **at start of Ph2** of  $E(NPV)$  is \$2B then since  $E(NPV)$  at that time is \$1.95B it is a marginal case for taking forward into Ph2

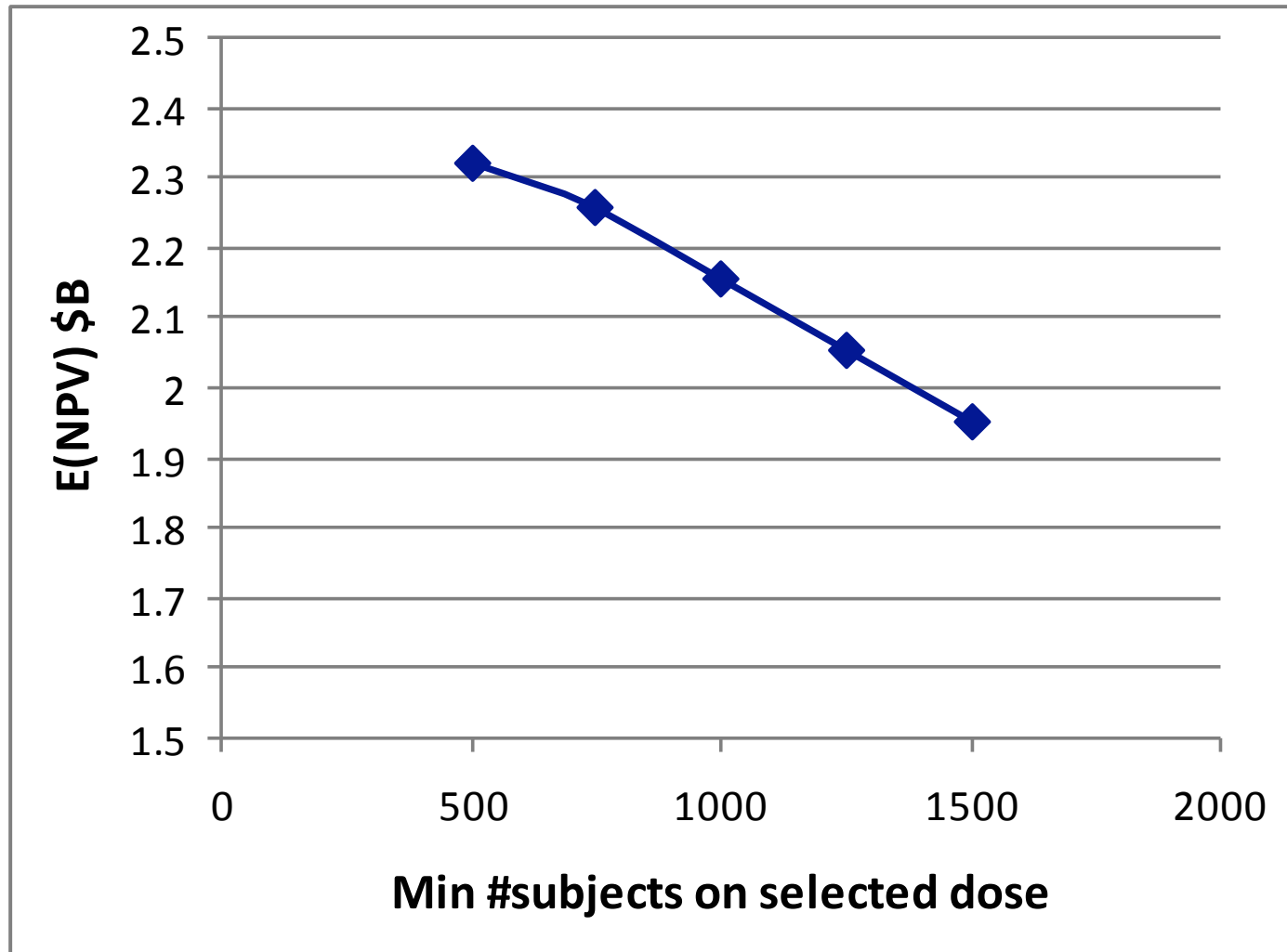
If hurdle value **at end of Ph 2** of  $E(NPV)$  is also \$2B to reflect opportunity cost then there is a 0.434 chance that we will not go on to Ph3

# Varying Ph2b Sample Size

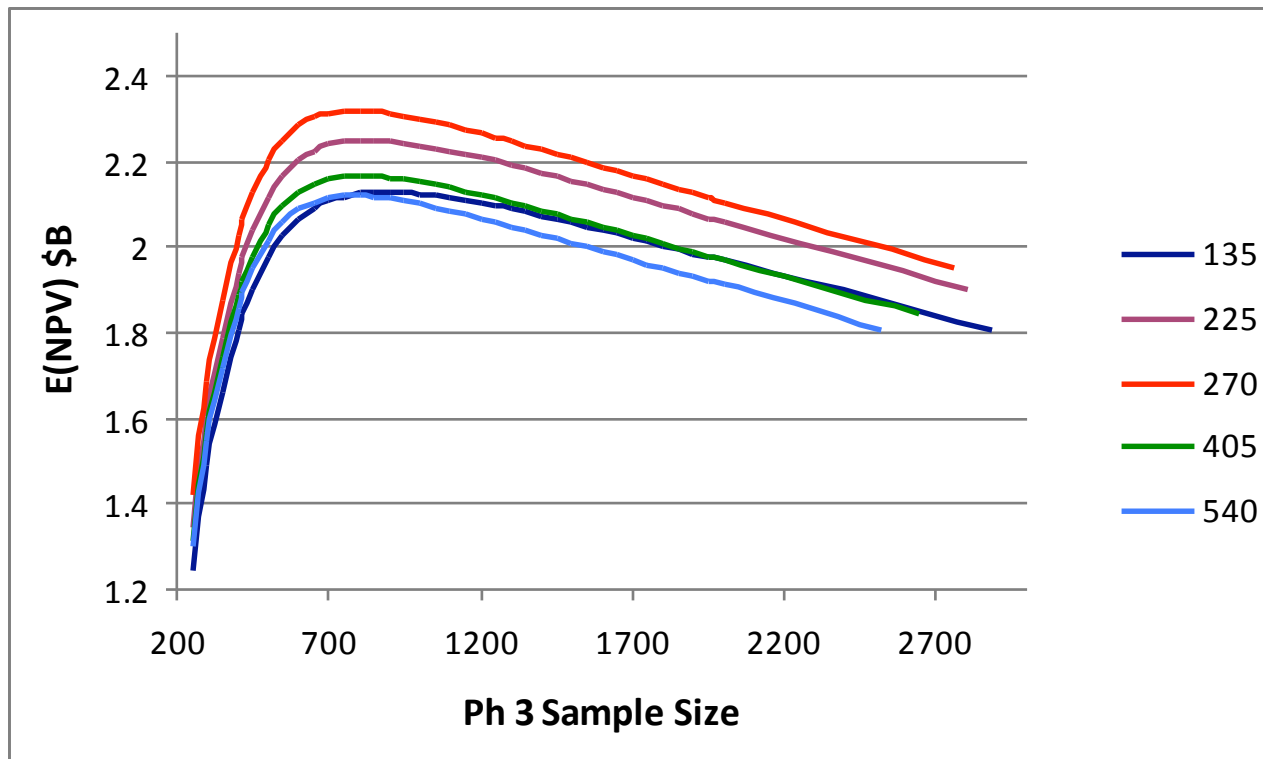
	Phase 2 Power	Prob. of going to Phase 3	Phase 3 Sample size if conducted	Prob. Phase 3 Success	Total Development Time (yrs)	Expected True Discounted NPV (\$B)
SS=15x9=135	0.82	0.75	2880	0.74	6.7	1.81
SS=25x9=225	0.95	0.79	2800	0.79	7.0	1.90
SS=30x9=270	0.97	0.80	2760	0.80	7.1	1.95
SS=45x9=405	0.99	0.84	2640	0.83	7.5	1.84
SS=60x9=540	0.99	0.87	2520	0.86	7.9	1.81

**Best PoS in Ph3 might not mean highest NPV**

# Reducing min # subjects in ICH guidance



# Optimizing Ph 2 and Ph 3 Sample Sizes without ICH guideline minimum



Optimum:  $E(\text{NPV}) = \$B 2.32$ , Sample Sizes: Ph2 = 270  
Ph3 = 800 (both trials)

# Base Case with low and flat Dose Response

Half_EFF	0.000	0.0005	0.017	0.108	0.289	0.427	0.501	0.535	0.550
Eff. Flat	0	0	0	0	0	0	0	0	0

	Phase 2 Power	Prob. of going to Phase 3	Prob. Phase 3 Success	Total Develop- ment Time (yrs)	Expected True NPV (\$B)
Efficacy	0.97	0.80	0.80	7.1	1.95
half_EFF	0.55	0.16	0.16	7.1	0.071
null	0.036	0.002	0.000001	7.1	-0.0017

# Concluding Remarks

Next Steps to extend simulation model (partial list):

- Compare effect of having 4 doses (instead of 8) in Ph2b trial
- Model safety explicitly:
  - simulate nuisance AE' s Ph2 and select doses to maximize ENPV estimates from Ph2b posterior distribution
  - Model serious AE' s (as described by Chris Jennison)
- Consider other traditional fixed designs for Ph 3 with more than one dose
- Extend commercial model to reflect situations when more than one dose is approved and marketed
- Evaluate adaptive and group sequential designs for both Ph2b and Ph 3
- Model uncertainty in 5<sup>th</sup> year sales forecast and recognize down-side risk by using measures other than E(NPV) to compare programs (e.g. probability of meeting target level of NPV, expected utility based on elicited utility function)
- Use prior for probability of different dose response scenarios (as described by Carl-Fredrik Burman and Chris Jennison)

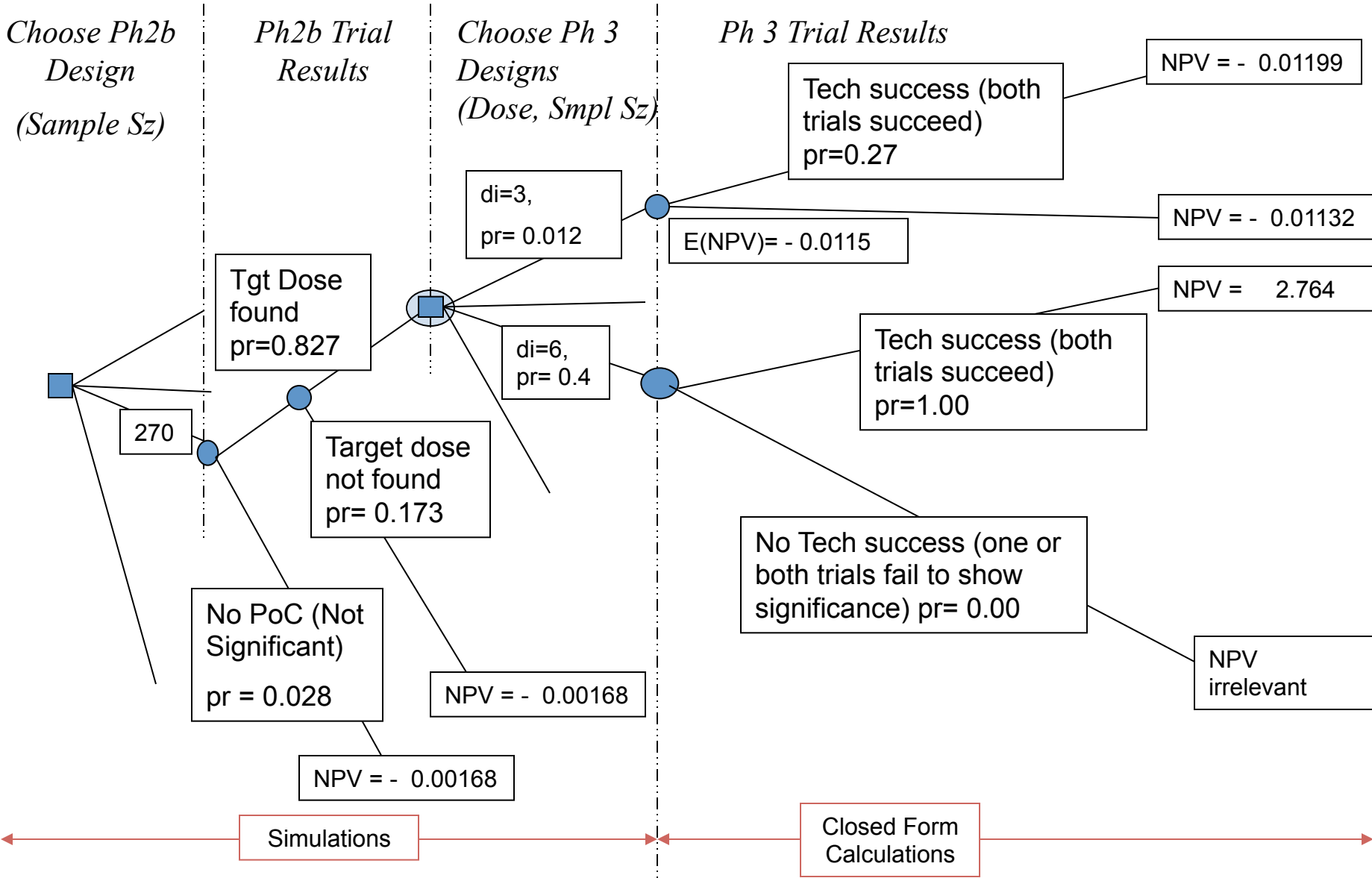
Explore opportunity to examine idea of Progressive Authorization that has been discussed at meetings at the Center for Biomedical Innovation at MIT with FDA Deputy Commissioner Dr. Murray Lumpkin, MD deputy commissioner, FDA

Thank you!

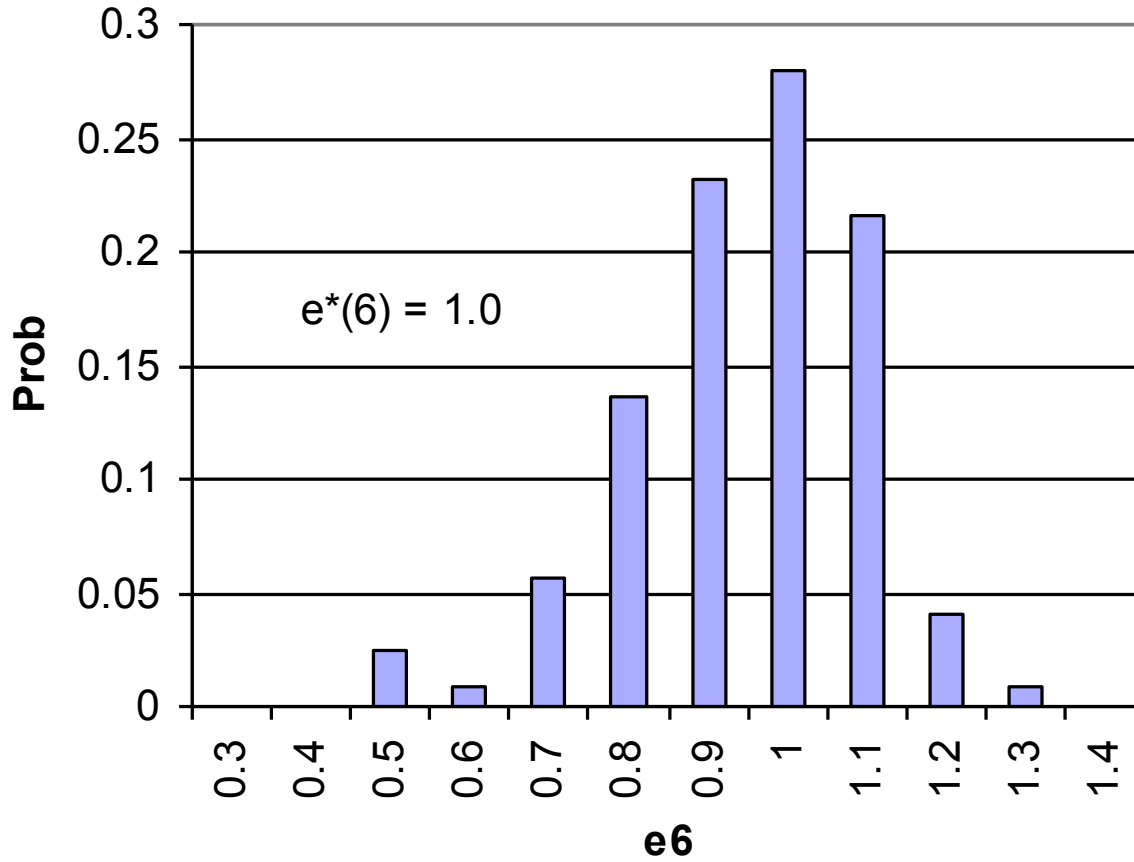
[nitin@cytel.com](mailto:nitin@cytel.com)

Extra Slides

# Decision Tree (Base Case, "Efficacy" DRCurve)



**Distribution of e6 when D6 was selected as Ph3 dose**



Mean	0.90
Median	0.92
Std Dev	0.14

# Accounting for downside risk

- Maximizing  $E(\text{NPV})$  does not model risk. If a utility function is elicited for NPV the availability of distribution of NPV enables calculation of utilities for different Ph2 and Ph3 sample sizes.
- Assessing utility function can be difficult. A satisficing criterion of maximizing the probability of meeting or exceeding a specified target NPV can reflect risk.
- If the target is \$B 0.8, Ph2 SS= 540 (pr = 0.86) is better than the ENPV maximizing SS of 270 (pr = 0.79).
- Can also use Target and linear loss functions on either side (Birge and Louveaux)

# Base Case (Efficacy DRCurve)

No dose selected	0.196
Dose selected	0.804
Pr(NoSignif)=	0.028
Pr(NoDoseSel Signif)=	0.173
Pr(Dose Found Signif)=	0.827
Pr( di =1 dose found)=	0.000
Pr( di =2 dose found)=	0.000
Pr( di =3 dose found)=	0.012
Pr( di =4 dose found)=	0.085
Pr( di =5 dose found)=	0.303
Pr( di =6 dose found)=	0.400
Pr( di =7 dose found)=	0.182
Pr( di =8 dose found)=	0.017