Extension of Neuropathic Pain Development Program Optimization by Considering 1 or 2 Doses in Phase 3

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Acknowledgement

Christy Chuang – Stein

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Late Drug Development Program for Neuropathic pain

- Investigate impact of various factors on PoS and NPV for a Ph2+Ph3 development program
  - Ph2 sample sizes
  - Number of Ph2 doses (4 or 8)
  - One or two doses in Ph3 trials
- Model permits study of many other factors
- Hybrid Bayesian/Frequentist approach
  - Statistical analysis of data from trial is frequentist, Go/NoGo decision making is Bayesian
  - Posterior distribution of mean response at each dose in Ph2 used to choose dose(s) for Ph3. Preposterior analysis to decide if 1 or 2 doses taken to Ph3 (Uninformative prior)
- Extension of work done by a Neuropathic Pain subteam of Adaptive Design Scientific Working Group

Ref: Patel N, et al. Designing phase 2 trials based on program-level considerations: A case study for neuropathic pain. *Drug Information Journal*, 46(4):439-454, 2012)

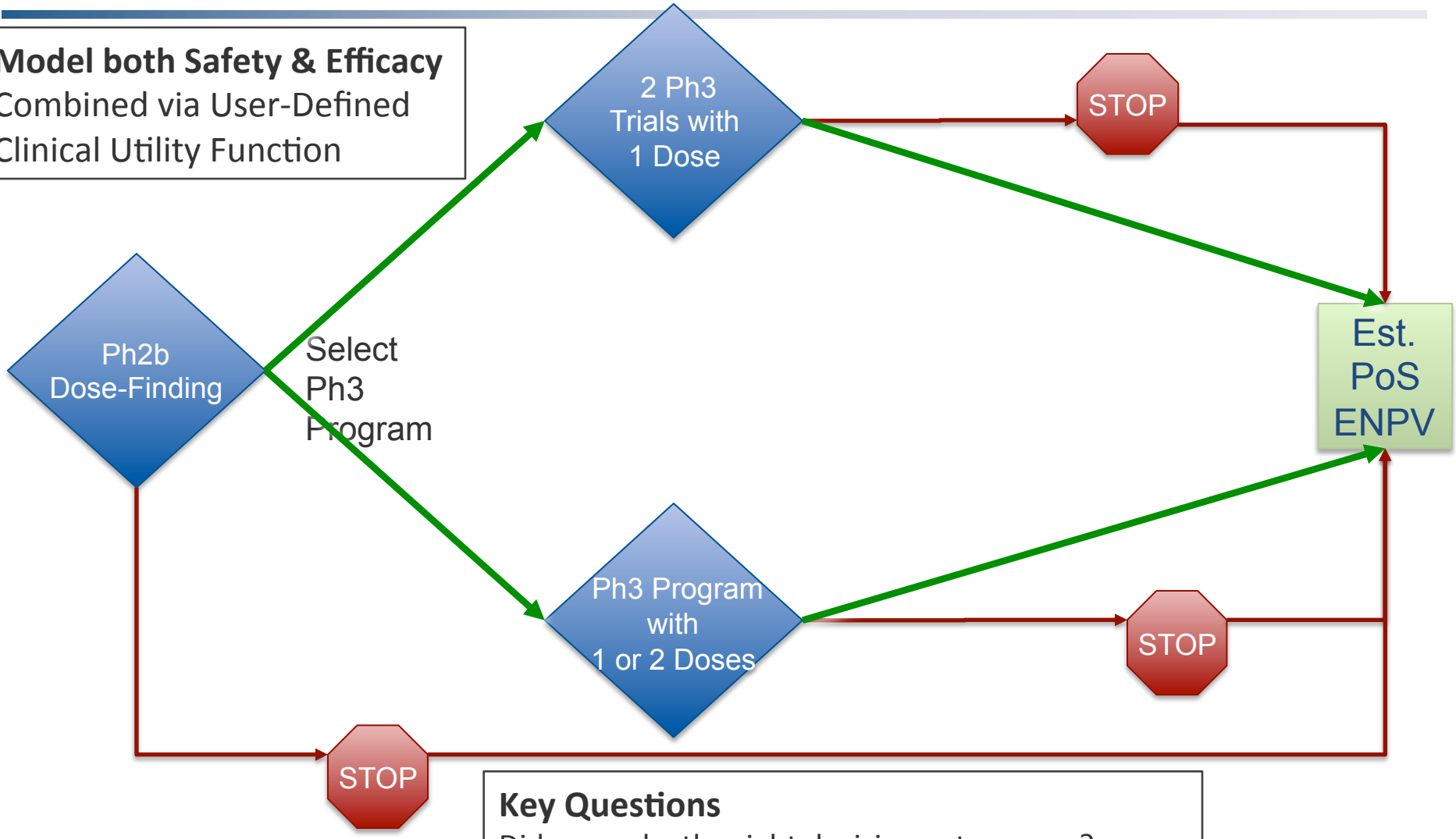
Performance Measures

Performance of designs assessed *at program level* by number of patients required, PoS, & profit.

- PoS measured by probability of 2 pivotal Phase 3 trials demonstrating statistically significant drug effect with observed mean response at least "delta."
- Profit measured by expected Net Present Value (eNPV).
- Magnitude of profit determined by relationship of efficacy and tolerability profile demonstrated by Ph3 trials to typical profits of comparator drugs and to trial costs
  - Via utility function developed with clinicians.

Ph2b→Ph3→NPV Simulation System

Model both Safety & Efficacy
Combined via User-Defined
Clinical Utility Function



Key Questions
Did we make the right decision - stop or go?
If go, did we get the Ph3 dose-choice right?
Did we optimize PoS ? NPV?

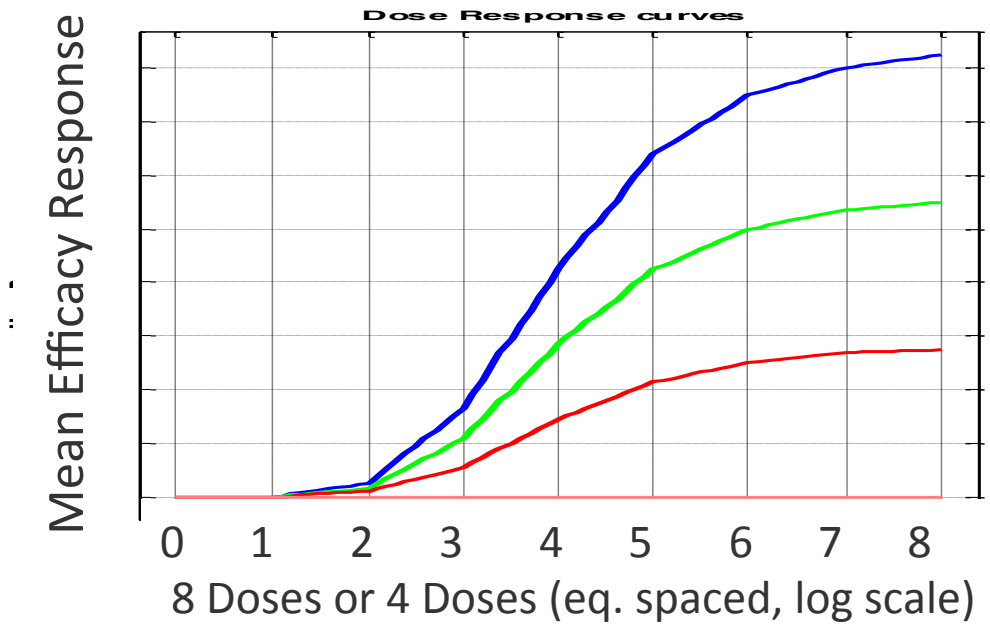
Criteria for taking dose(s) into Ph3

- For Phase 3: Minimum dose with posterior estimate of efficacy at least 1 unit better than placebo (D_i), else no dose for Ph3
- Dose is "Safe" if estimated AE rate < 0.3 using isotonic regression
- Take 1 dose (D_i) to Ph3 if D_{i+1} is not "safe"
- Take 2 doses (D_i and D_{i+1}) if D_{i+1} is "safe".

Design options for Ph3 (initial twin trials)

- Design 1
  - Two concurrent balanced Ph3 trials (Placebo and D_i)
  - Sample size based on power = 0.95
- Design 2
  - Two concurrent balanced Ph3 trials (Placebo, D_i and D_{i+1})
  - Sample size based on power = 0.95
    - adjusted, if Ph2 shows incremental efficacy to show incremental efficacy in Ph3 with pr 0.9 for mean efficacy difference between D_i and D_{i+1} of 0.5
    - if Ph2 does not show incremental efficacy adjust to yield 95% CI for difference in efficacy between D_i and D_{i+1} that excludes 0 or delta
  - Incremental Efficacy definition: Point estimate for efficacy difference between D_i and $D_{i+1} \geq 0.5$ AND lower limit of 95% CI > 0
- Design 12
  - Select Design 1 or Design 2 based on predicted eNPV (preposterior analysis)

Scenarios: Sigmoid Emax Dose Response, monotone AE profile



High Efficacy (max=2.2)

Medium Efficacy (max=1.65)

Low Efficacy (max=1.1)

No Efficacy (min=0)

Std.Dev. = 2 for Ph2; 2.5 for Ph3

AE Rates

AE Profile	D0	D1	D2	D3	D4	D5	D6	D7	D8
Low	0.10	0.10	0.10	0.10	0.10	0.10	0.125	0.15	0.175
Moderate	0.10	0.10	0.10	0.10	0.15	0.20	0.25	0.30	0.35
High	0.10	0.15	0.15	0.15	0.225	0.30	0.375	0.45	0.525

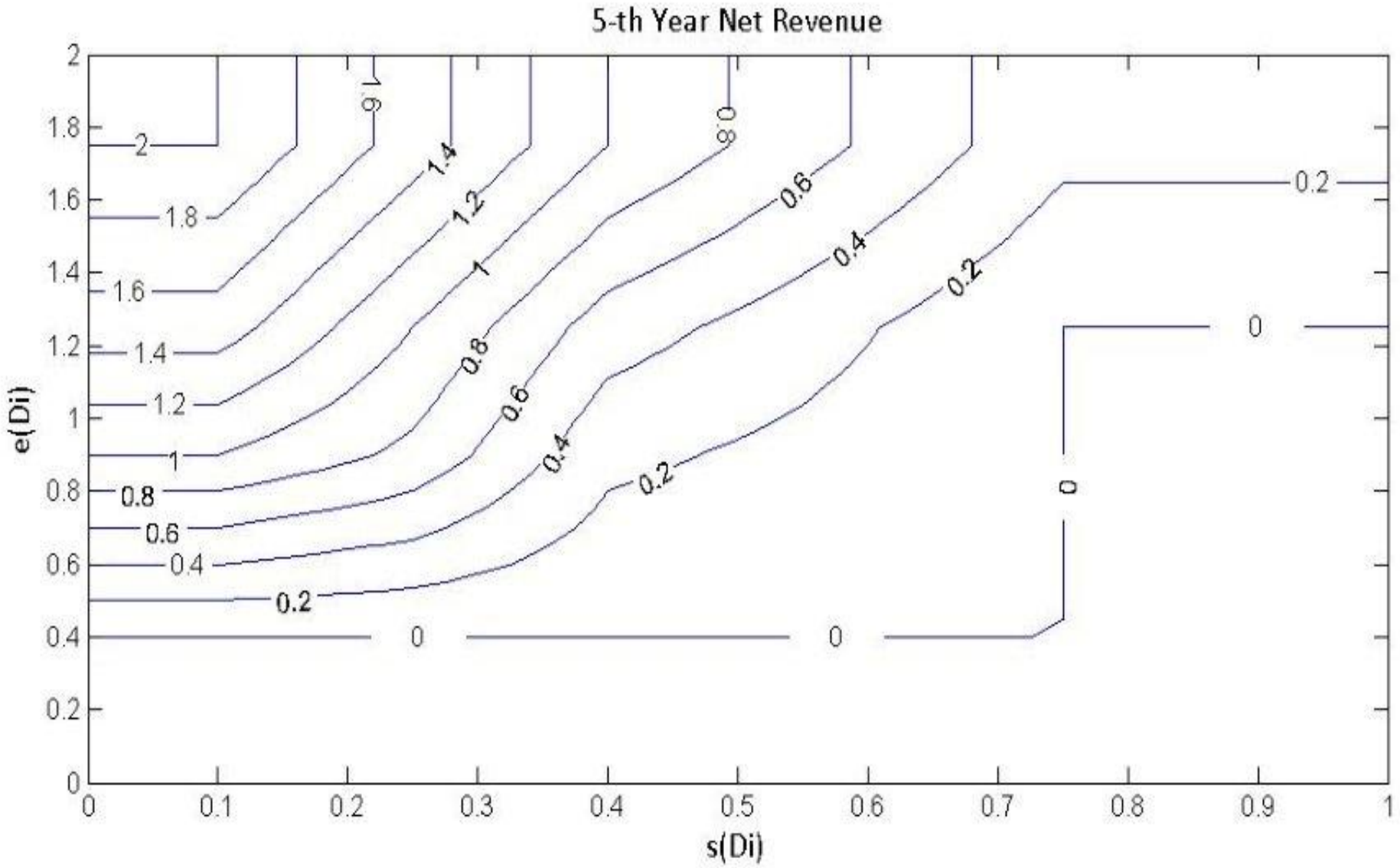
1000 Ph2 trial simulations used for each scenario

Clinical Utility assessment

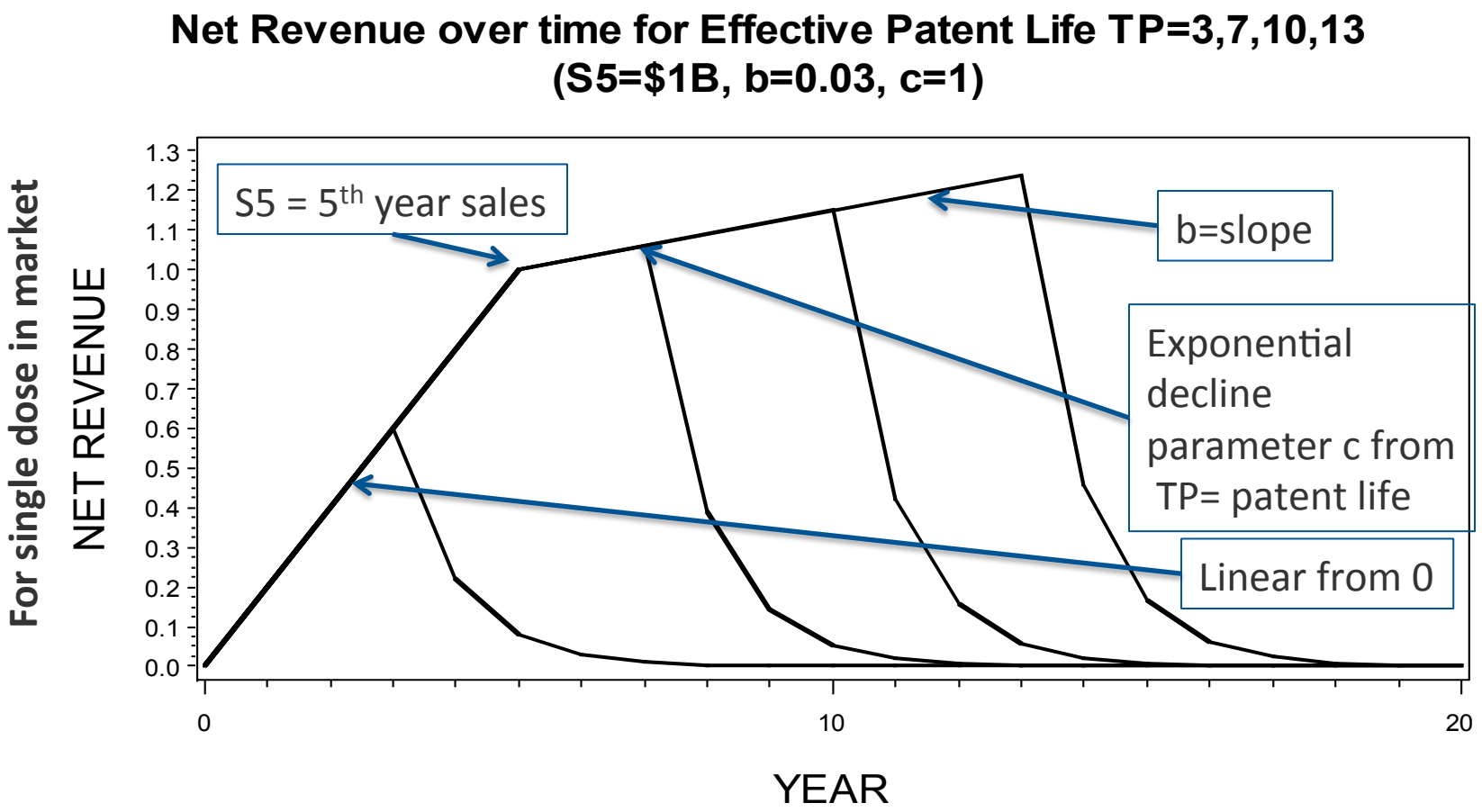
$e(D_i)$=efficacy diff. from placebo for dose Di
$s(D_i)$=AE rate for dose Di

Efficacy compared to marketed products	Tolerability compared to marketed products			
	Better: $s(D_i) < 0.2$	Similar: $0.2 \le s(D_i) < 0.3$	Worse: $0.3 \le s(D_i) \le 0.5$	Stop program: $s(D_i) > 0.5$
Better $1.5 \le e(D_i)$	2.00	1.50	1.00	0.25
Similar: $1.0 \le e(D_i) < 1.5$	1.50	1.00	0.50	0.00
Worse: $0.8 < e(D_i) < 1.0$	1.00	0.75	0.25	0.00
Stop program: $e(D_i) < 0.8$	0.00	0.00	0.00	0.00

5th year Net Revenue α Clinical Utility



Time profile of Net Revenue



Net revenue from 2 doses in market reduced from sum of single dose values:

- $S5_{2doses} = k_1 * S5_{Di} + k_2 * S5_{Di+1}$
- Base Case: $k_1 = 0.75 + k_2 = 0.75$
- Fixed Manufacturing Investment increased 2-fold

Expected NPV ($B)
Single Ph3 dose (Design 1)

Optimum ENPV's highlighted

Max Efficacy Response	AE Profile	Ph2 Sample Size						
		135	225	270	405	540	675	810
SigmoidEmax_1.1	High	0.429	0.355	0.414	0.322	0.294	0.259	0.226
SigmoidEmax_1.1	Moderate	1.126	1.060	1.175	1.059	1.050	0.916	0.918
SigmoidEmax_1.1	Low	2.240	2.364	2.488	2.410	2.331	2.197	2.174
SigmoidEmax_1.65	High	2.197	2.373	2.415	2.489	2.527	2.325	2.202
SigmoidEmax_1.65	Moderate	3.618	3.847	3.919	3.796	3.611	3.361	3.101
SigmoidEmax_1.65	Low	5.504	5.487	5.436	5.071	4.684	4.329	3.973
SigmoidEmax_2.2	High	4.228	4.286	4.451	4.160	3.878	3.594	3.270
SigmoidEmax_2.2	Moderate	5.372	5.332	5.316	4.890	4.495	4.122	3.760
SigmoidEmax_2.2	Low	6.535	6.371	6.259	5.692	5.181	4.745	4.322

Expected NPV ($B)
Design 12: one or two doses based on preposterior analysis

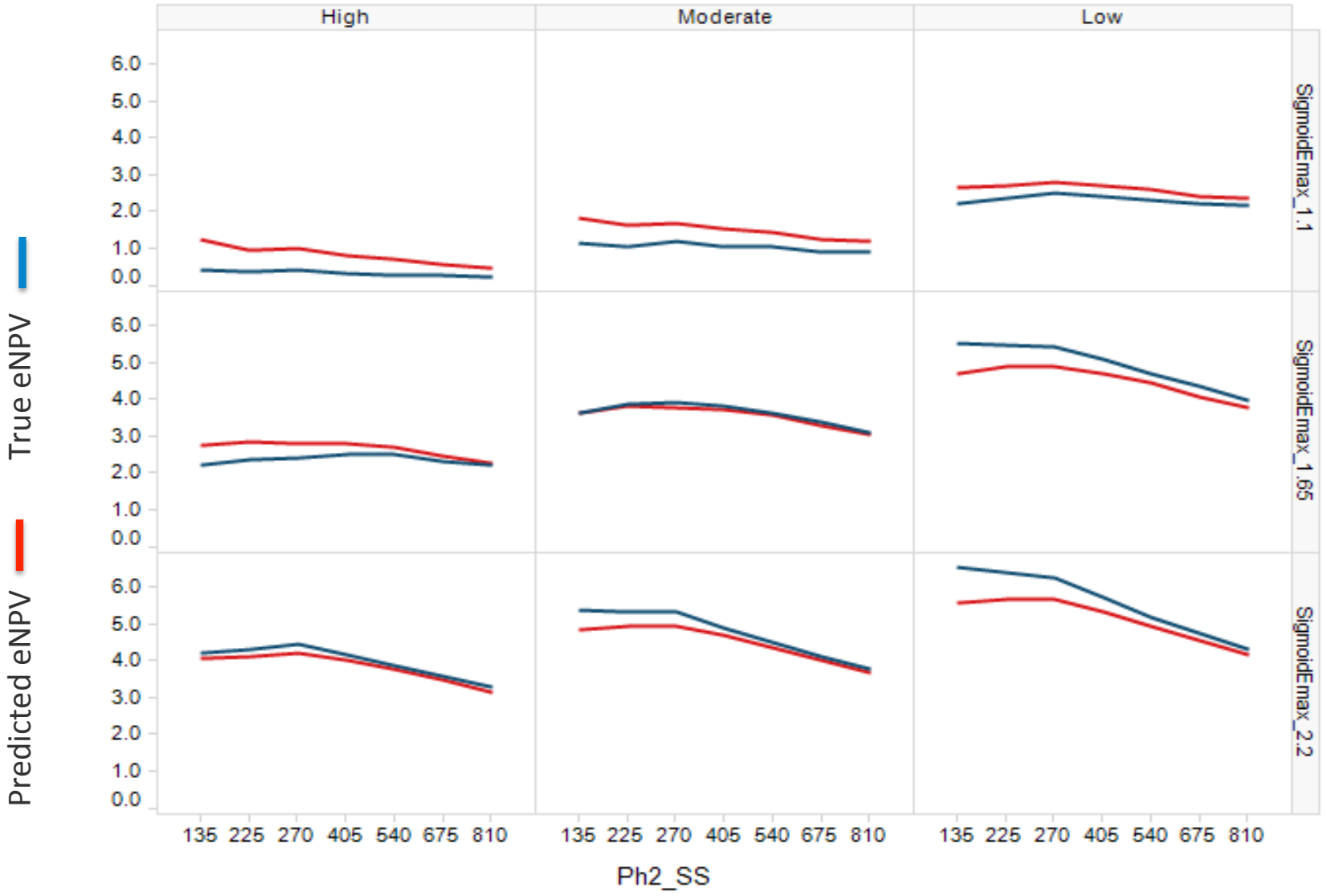
Cytel

Optimum ENPV's highlighted

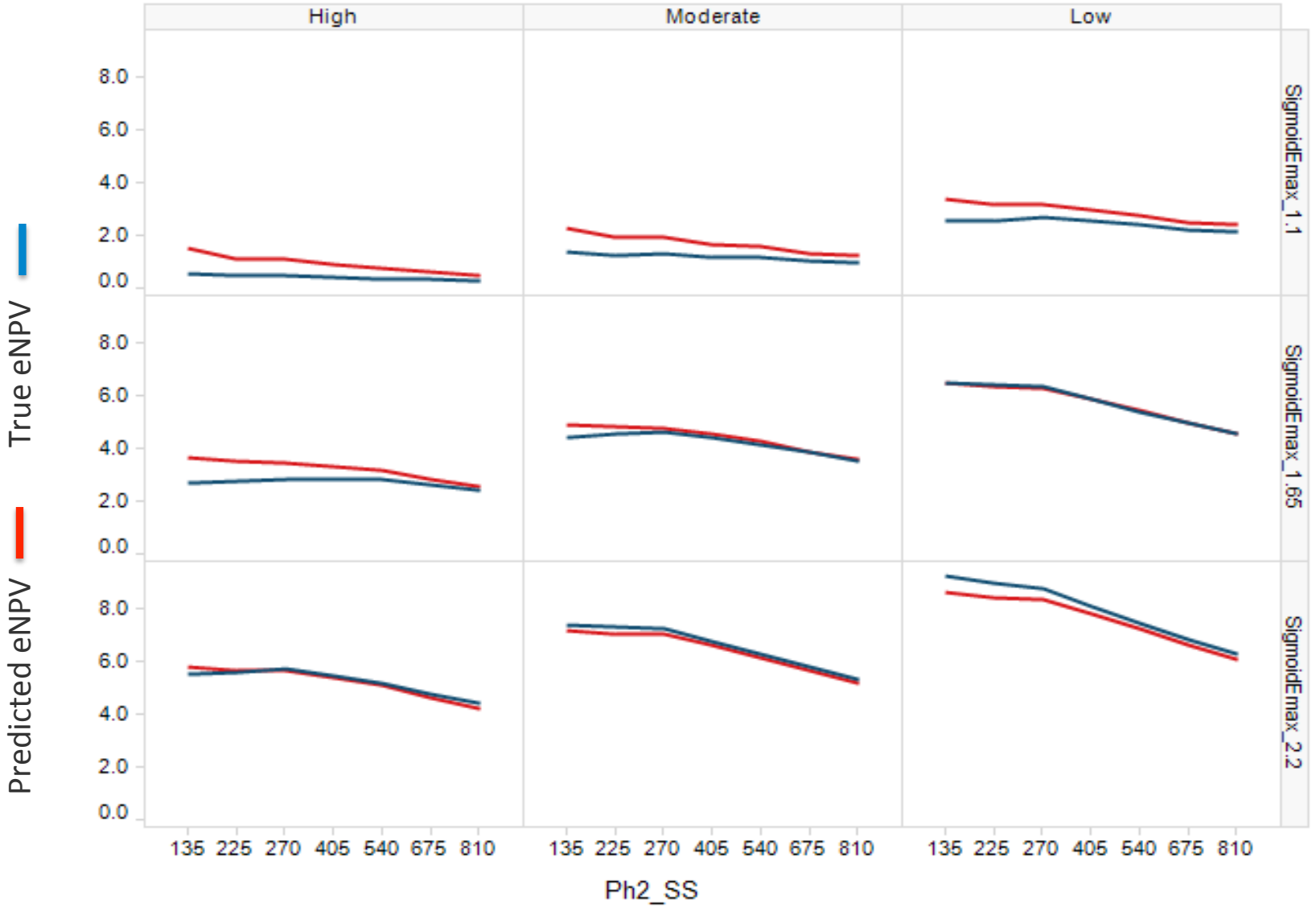
Max Efficacy Response	AE Profile	Ph2 Sample Size						
		135	225	270	405	540	675	810
SigmoidEmax_1.1	High	0.548	0.437	0.483	0.381	0.338	0.288	0.243
SigmoidEmax_1.1	Moderate	1.339	1.226	1.317	1.163	1.124	0.973	0.946
SigmoidEmax_1.1	Low	2.521	2.558	2.651	2.504	2.391	2.243	2.206
SigmoidEmax_1.65	High	2.647	2.753	2.820	2.817	2.805	2.585	2.422
SigmoidEmax_1.65	Moderate	4.383	4.538	4.606	4.413	4.148	3.828	3.499
SigmoidEmax_1.65	Low	6.501	6.406	6.335	5.906	5.419	4.970	4.530
SigmoidEmax_2.2	High	5.548	5.598	5.733	5.433	5.170	4.756	4.389
SigmoidEmax_2.2	Moderate	7.419	7.306	7.253	6.772	6.295	5.781	5.292
SigmoidEmax_2.2	Low	9.279	8.996	8.803	8.128	7.486	6.864	6.279

All greater than those of Design1 (2% to 45%)

Design 1


High
Moderate
Low
SigmoidEmax_1.1
SigmoidEmax_1.65
SigmoidEmax_2.2
True eNPV
Predicted eNPV
6.0
5.0
4.0
3.0
2.0
1.0
0.0
135 225 270 405 540 675 810
Ph2_SS

Design 2


High
Moderate
Low
SigmoidEmax_1.1
SigmoidEmax_1.65
SigmoidEmax_2.2
True eNPV
Predicted eNPV
8.0
6.0
4.0
2.0
0.0
135 225 270 405 540 675 810
Ph2_SS

%eNPV improvement for Sample Size=270 compared to other SS (Moderate AE rate)

K1=	0.75	K2									
DR_Curve	Ph2_SS	0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.25	2.5
SigmoidEmax_1.1	135	-1%	-1%	-2%	-2%	-3%	-3%	-4%	-4%	-5%	-5%
SigmoidEmax_1.1	225	8%	7%	7%	7%	6%	6%	6%	6%	5%	5%
SigmoidEmax_1.1	270	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
SigmoidEmax_1.1	405	11%	11%	11%	11%	11%	11%	11%	11%	11%	11%
SigmoidEmax_1.1	540	13%	13%	14%	14%	14%	15%	15%	15%	16%	16%
SigmoidEmax_1.1	675	25%	25%	25%	25%	26%	26%	26%	26%	26%	27%
SigmoidEmax_1.1	810	26%	27%	27%	28%	28%	29%	29%	30%	30%	31%
SigmoidEmax_1.65	135	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
SigmoidEmax_1.65	225	1%	1%	1%	2%	2%	2%	2%	2%	2%	2%
SigmoidEmax_1.65	270	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
SigmoidEmax_1.65	405	5%	5%	4%	4%	3%	3%	3%	3%	2%	2%
SigmoidEmax_1.65	540	11%	10%	10%	9%	9%	9%	8%	8%	8%	8%
SigmoidEmax_1.65	675	18%	17%	17%	16%	16%	16%	15%	15%	15%	15%
SigmoidEmax_1.65	810	25%	24%	24%	24%	23%	23%	23%	22%	22%	22%
SigmoidEmax_2.2	135	-5%	-3%	-2%	-1%	-1%	0%	0%	1%	1%	1%
SigmoidEmax_2.2	225	-1%	-1%	-1%	-1%	0%	0%	0%	0%	0%	0%
SigmoidEmax_2.2	270	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
SigmoidEmax_2.2	405	9%	8%	7%	6%	6%	5%	5%	5%	4%	4%
SigmoidEmax_2.2	540	16%	14%	13%	12%	11%	11%	10%	10%	10%	9%
SigmoidEmax_2.2	675	23%	22%	20%	19%	19%	18%	18%	17%	17%	17%
SigmoidEmax_2.2	810	30%	28%	27%	26%	25%	25%	24%	24%	24%	24%

Comparing 4 and 8 doses: sample sizes *not dependent* on knowledge of scenario

Max Efficacy response	AE Profile	Optimum Ph 2 (4 Doses)			Optimum Ph 2 (8 Doses)			PoS % Improvement	ENPV % Improvement
		Sample size	Prob. of Success	Expected NPV ($B)	Sample size	Prob. of Success	Expected NPV ($B)		
SigmoidEmax_1.1	High	135	0.09	0.19	270	0.20	0.48	112	150
SigmoidEmax_1.1	Moderate	135	0.35	1.16	270	0.45	1.32	29	13
SigmoidEmax_1.1	Low	135	0.61	2.78	270	0.68	2.65	11	-5
SigmoidEmax_1.65	High	135	0.34	1.31	270	0.68	2.82	100	116
SigmoidEmax_1.65	Moderate	135	0.76	4.18	270	0.92	4.61	21	10
SigmoidEmax_1.65	Low	135	0.94	6.94	270	0.99	6.33	5	-9
SigmoidEmax_2.2	High	135	0.62	3.23	270	0.93	5.73	49	77
SigmoidEmax_2.2	Moderate	135	0.91	6.63	270	0.99	7.25	9	9
SigmoidEmax_2.2	Low	135	1.00	9.44	270	1.00	8.80	0	-7

PoS is better for 8 doses under all scenarios

Unless Low AE scenario is very likely, 8 doses are much better than 4 doses.

Summary Remarks & Conclusions

- Ph2 sample size can be optimized to yield maximum eNPV when 1 or 2 doses could be selected for Ph3 development.
- eNPV from program design taking 1 or 2 doses into Ph3 is higher than if only one dose is chosen.
- Optimum Ph2 sample size is robust to parameters used to combine individual net revenue sales functions into net revenue if two doses are marketed.
- Using 8 doses in Ph2 gives higher PoS than 4 doses for all scenarios studied
- Using 8 doses in Ph2 gives higher eNPV than 4 doses unless AE rates are low for all doses
  - Highlights potential advantage of adaptive Ph2 design
- Limitations: Above confined to
  - eNPV model assumed
  - Specific efficacy and safety dose-response models studied
- Framework can be applied to specific development programs to augment information base for strategic decision-making using models that are appropriate for other therapeutic areas.

Thank you

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Comparing 4 and 8 doses: Optimum sample sizes for each scenario

Design12									
Max Efficacy response	AE Profile	Optimum Ph 2 SS (4 Doses)			Optimum Ph 2 SS (8 Doses)			Ph3 PoS % Improvement	ENPV % Improvement
		Sample size	Prob. Of Ph3 Success	Expected NPV ($B)	Sample size	Prob. Of Ph3 Success	Expected NPV ($B)		
SigmoidEmax_1.1	High	135	0.095	0.195	135	0.220	0.548	131%	182%
SigmoidEmax_1.1	Moderate	135	0.348	1.166	135	0.436	1.339	25%	15%
SigmoidEmax_1.1	Low	135	0.615	2.788	270	0.680	2.651	11%	-5%
SigmoidEmax_1.65	High	135	0.344	1.311	270	0.685	2.824	99%	115%
SigmoidEmax_1.65	Moderate	270	0.844	4.318	270	0.922	4.608	9%	7%
SigmoidEmax_1.65	Low	135	0.945	6.943	135	0.947	6.501	0%	-6%
SigmoidEmax_2.2	High	135	0.623	3.232	270	0.928	5.739	49%	78%
SigmoidEmax_2.2	Moderate	135	0.908	6.648	135	0.963	7.419	6%	12%
SigmoidEmax_2.2	Low	135	0.997	9.442	135	0.996	9.279	0%	-2%

Comparing 4 and 8 doses: sample sizes *not dependent* on knowledge of scenario

Max Efficacy response	AE Profile	Optimum Ph 2 (4 Doses)			Optimum Ph 2 (8 Doses)			PoS % Improvement	ENPV % Improvement
		Sample size	Prob. of Success	Expected NPV ($B)	Sample size	Prob. of Success	Expected NPV ($B)		
SigmoidEmax_1.1	High	135	0.09	0.19	135	0.22	0.55	134	184
SigmoidEmax_1.1	Moderate	135	0.35	1.16	135	0.44	1.34	25	15
SigmoidEmax_1.1	Low	135	0.61	2.78	135	0.62	2.52	0	-9
SigmoidEmax_1.65	High	135	0.34	1.31	135	0.60	2.65	76	103
SigmoidEmax_1.65	Moderate	135	0.76	4.18	135	0.82	4.38	7	5
SigmoidEmax_1.65	Low	135	0.94	6.94	135	0.95	6.50	0	-6
SigmoidEmax_2.2	High	135	0.62	3.23	135	0.86	5.55	38	72
SigmoidEmax_2.2	Moderate	135	0.91	6.63	135	0.96	7.42	6	12
SigmoidEmax_2.2	Low	135	1.00	9.44	135	1.00	9.28	0	-2

PoS is better for 8 doses under all scenarios

Unless Low AE scenario is very likely, 8 doses are better than 4 doses.

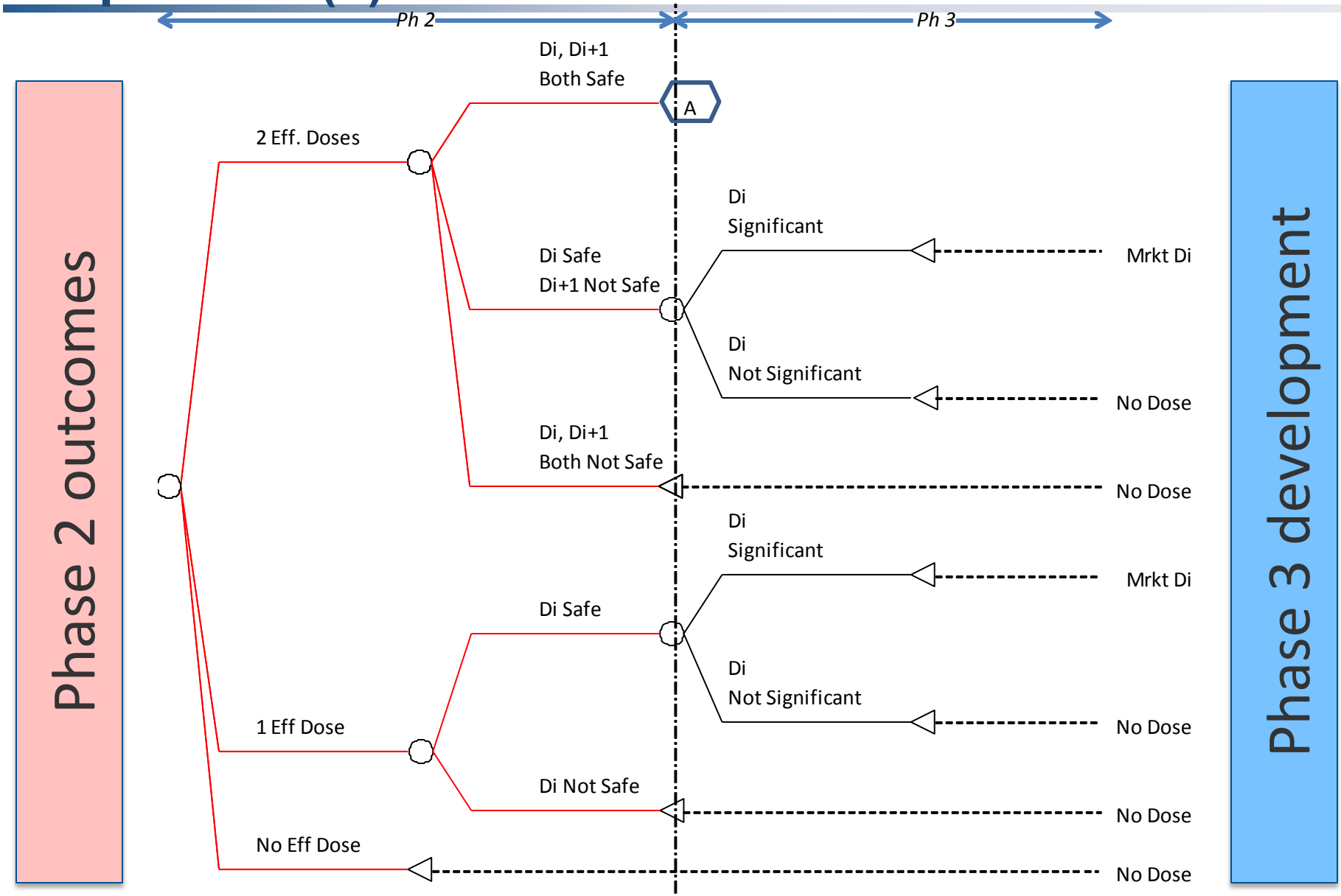
Comparing 4 and 8 doses: sample sizes *not dependent* on knowledge of scenario

Max Efficacy response	AE Profile	Optimum Ph 2 (4 Doses)			Optimum Ph 2 (8 Doses)			PoS % Improvement	ENPV % Improvement
		Sample size	Prob. of Success	Expected NPV ($B)	Sample size	Prob. of Success	Expected NPV ($B)		
SigmoidEmax_1.1	High	270	0.07	0.15	270	0.20	0.48	170	226
SigmoidEmax_1.1	Moderate	270	0.35	1.10	270	0.45	1.32	29	20
SigmoidEmax_1.1	Low	270	0.64	2.71	270	0.68	2.65	6	-2
SigmoidEmax_1.65	High	270	0.34	1.19	270	0.68	2.82	103	136
SigmoidEmax_1.65	Moderate	270	0.84	4.32	270	0.92	4.61	9	7
SigmoidEmax_1.65	Low	270	0.99	6.65	270	0.99	6.33	0	-5
SigmoidEmax_2.2	High	270	0.65	3.11	270	0.93	5.73	42	85
SigmoidEmax_2.2	Moderate	270	0.93	6.43	270	0.99	7.25	7	13
SigmoidEmax_2.2	Low	270	1.00	8.87	270	1.00	8.80	0	-1

PoS is better for 8 doses under all scenarios

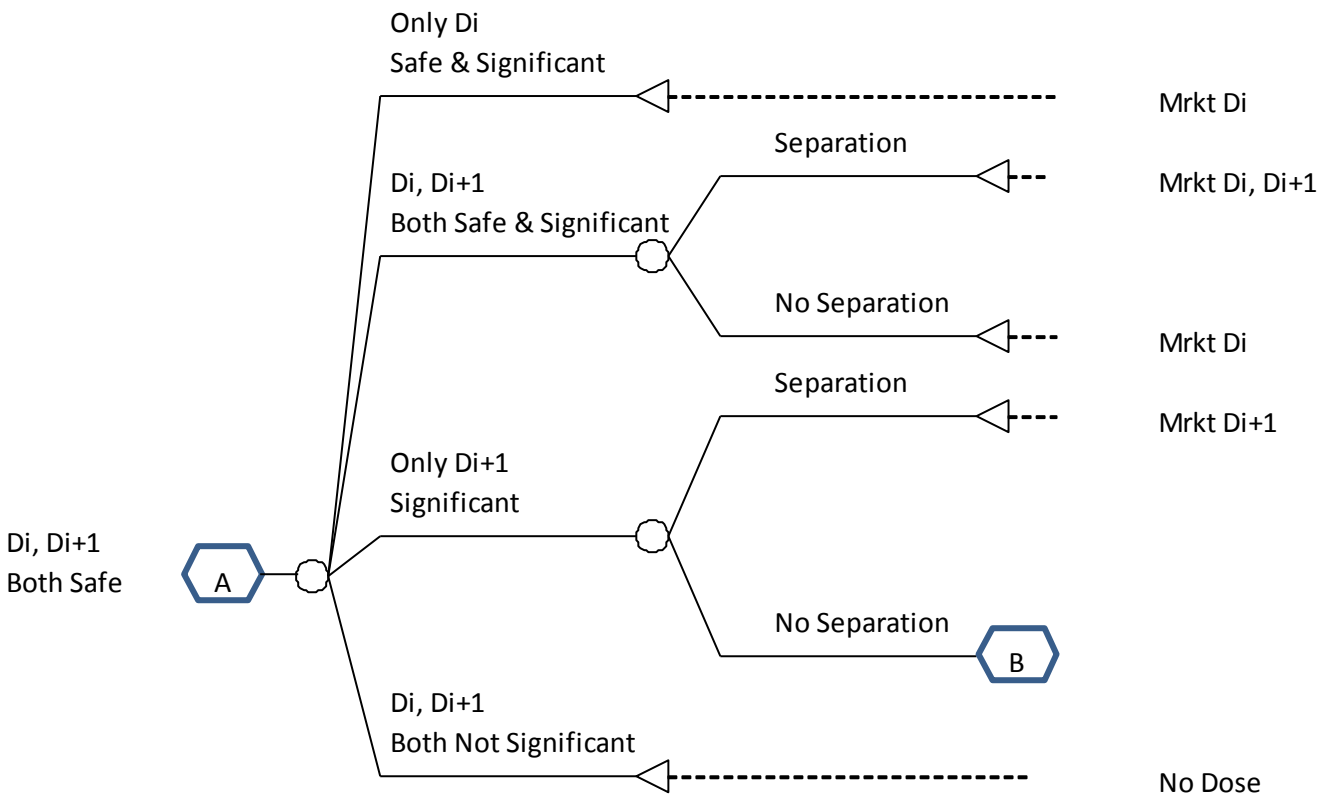
Unless Low AE scenario is very likely, 8 doses are better than 4 doses.

Decision tree showing Ph3 development sequences (1)



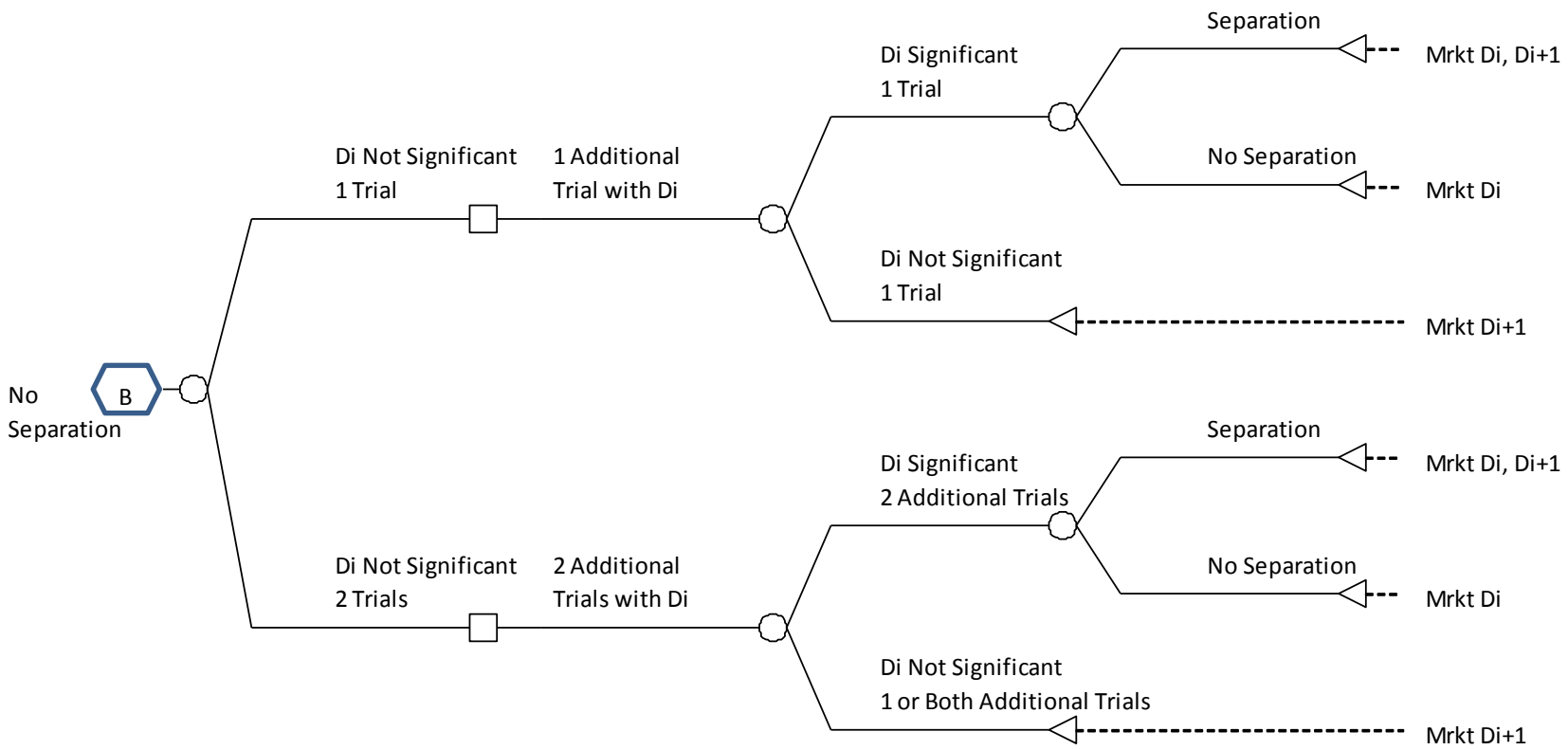
Decision tree showing Ph3 development sequences (2)

Phase 3 development



Decision tree showing Ph3 development sequences (3)

Phase 3 development



Ratio of eNPV's (Design 12 / Design1)

Max Efficacy Response	AE Profile	Ph2 Sample Size						
		135	225	270	405	540	675	810
SigmoidEmax_1.1	High	1.279	1.230	1.164	1.183	1.150	1.110	1.076
SigmoidEmax_1.1	Moderate	1.189	1.156	1.121	1.098	1.070	1.062	1.031
SigmoidEmax_1.1	Low	1.125	1.082	1.065	1.039	1.026	1.021	1.015
SigmoidEmax_1.65	High	1.205	1.160	1.168	1.132	1.110	1.112	1.100
SigmoidEmax_1.65	Moderate	1.211	1.179	1.175	1.163	1.149	1.139	1.129
SigmoidEmax_1.65	Low	1.181	1.167	1.165	1.165	1.157	1.148	1.140
SigmoidEmax_2.2	High	1.312	1.306	1.288	1.306	1.333	1.324	1.342
SigmoidEmax_2.2	Moderate	1.381	1.370	1.364	1.385	1.401	1.403	1.407
SigmoidEmax_2.2	Low	1.420	1.412	1.406	1.428	1.445	1.447	1.453

Design12 is better than Design 1 for all scenarios and Ph2 sample sizes