Pulmonary Embolism

tPA vs. TNKs

Dose Finding

Study Basics

- Control Arm vs. 5 arms of TNK
- Endpoint is Success at 6 months
  - No pulmonary hypertension
  - Observe S/F at 1 month
- CSD For trial design is 7.5%
- Maximum Sample size of 300
- Accrue 3:6 Control

Design

- First Interim at 100
  - 25, 15, 15, 15, 15, 15
- Interims every 12 weeks
- Adjust randomization probabilities
  - Proportional to prob each dose is the ED90
- Stop for futility if most likely ED90 has prob > CSD < 0.10
- Stop for success if prob > control > 0.99
  - Based on DR and LM

Modeling

- Longitudinal Modeling
  - For subjects with partial information we “impute” the final 6 month data from 1-month outcome
  - Separate Instances for tPA or TNK
  - Priors:

$$P(S \mid M_1 = S) \sim Beta(99,1)$$

$$P(S \mid M_1 = F) \sim Beta(3,5)$$

Modeling

- Dose-Response Modeling
  - Model Control with flat prior (not part of DR)
  - Model DR with Hierarchical-Sigmoid

$$\log\left(\frac{\pi_d}{1-\pi_d}\right) = \alpha_1 + \alpha_2\left(\frac{v_d}{v_d+\alpha_3}\right) + \delta_d$$

$$[\delta_d] \sim N(0, \tau^2) \qquad \tau^2 \sim IG(0.1,1)$$

	SS	Power	Futility	Control	1	2	3	4	5
Null	258	.09	.59	75 78	75 56 .30	75 25 .02	75 25 .01	75 30 .04	75 44 .17
Flat80	273	.29	.30	75 83	80 63 .46	80 26 .02	80 26 .03	80 33 .09	80 41 .22
Flat85	264	.69	.10	75 80	85 67 .62	85 27 .03	85 26 .03	85 31 .13	85 34 .14
Flat90	244	.93	.02	75 73	90 63 .70	90 25 .02	90 26 .07	90 29 .14	90 27 .06

	SS	Power	Futility	Control	1	2	3	4	5
Linear85	272	.50	.15	75 82 .18	77 44 .18	79 24 .02	81 25 .03	83 38 .12	85 57 .57
Linear90	258	.84	.03	75 78	78 36 .10	81 22 .01	84 26 .03	87 40 .24	90 56 .61
Plateau85	272	.57	.11	75 82	78 43 .18	80 25 .02	82 27 .02	85 40 .22	85 55 .49
Plateau90	252	.90	.02	75 76	79 36 .09	82.5 22 .01	86 27 .03	90 42 .40	90 49 .46

Accrual

	A/yr	SS	Power	Futility	Control	1	2	3	4	5
Null	50	244	.07	.62	75 73	75 54 0.3	75 25 .02	75 24 .01	75 29 .04	75 39 .16
Null	100	258	.09	.59	75 78	75 56 .30	75 25 .02	75 25 .01	75 30 .04	75 44 .17
Null	200	271	.10	.54	75 82	75 64 .38	75 26 .02	75 25 .02	75 31 .05	75 43 .17
Linear 90	50	242	.82	.06	75 72	78 33 .09	81 21 .004	84 25 .02	87 38 .24	90 52 .59
Linear 90	100	258	.84	.03	75 78	78 36 .10	81 22 .01	84 26 .03	87 40 .24	90 56 .61
Linear 90	200	276	.83	.05	75 84	78 44 .09	81 23 .01	84 27 .02	87 41 .21	90 57 .65

Longitudinal Modeling

		SS	Power	Futility	Control	1	2	3	4	5
Null	None	281	.22	.42	85	56 .41	29 .02	29 .03	34 .05	47 .20
Null	Long. Model	258	.09	.59	78	56 .30	25 .02	25 .01	30 .04	44 .17
Null	Perfect	252	.08	.55	76	57 .26	25 .03	24 .02	29 .03	41 .20
Linear 90	None	252	.87	.04	76	44 .14	27 .01	27 .02	34 .23	45 .58
Linear 90	Long. Model	258	.84	.03	78	36 .10	22 .01	26 .03	40 .24	56 .61
Linear 90	Perfect	249	.87	.02	75	30 .08	21 .01	25 .03	40 .24	58 .64

Modeling + Response Adaptive Randomization

		SS	Power	Futility	Control	1	2	3	4	5
Null	Model/ RAR	258	.09	.59	75 78	75 56 .30	75 25 .02	75 25 .01	75 30 .04	75 44 .17
Null	Model/ Fixed	261	.08	.45	65	39 .36	39 .02	39 .01	39 .04	39 .18
Null	None/ RAR	283	.17	.29	86	42 .20	40 .17	40 .17	37 .13	38 .17
Null	None/Fixed	283	.24	.21	71	42 .23	42 .18	42 .15	42 .16	42 .15
Linear 90	Model/ RAR	258	.84	.03	75 78	78 36 .10	81 22 .01	84 26 .03	87 40 .24	90 56 .61
Linear 90	Model/ Fixed	264	.76	.05	66	40 .12	40 0.00	40 .02	40 .24	40 .59
Linear 90	None/ RAR	262	.87	.01	79	28 .03	30 .07	37 .14	41 .26	48 .49
Linear 90	None/ Fixed	262	.86	.01	66	39 .04	39 .08	39 .14	39 .28	39 .45

Pulmonary Embolism

tPA vs. TNKs

Enrichment

Fixed Design

- Enroll Subjects in both groups
  - 67% Low; 33% high
  - 100/yr accrual
- Futility @ 100, every 3 months
  - Stop if <10% chance > 7.5% benefit (all)
- 300 subjects total, 1:1 randomization
- Do final analysis of effect in all subjects
  - Use group as covariate, but no interaction allowed
- Final analysis when data complete

Results

Low	High	Mean N	High N	Pr(Win)	Pr(Enrich)	Pr(Futility)
.80/.80	.60/.60	191.8	63.6	0.048	0	0.694
.80/.80	.60/.75	237.9	79.3	0.224	0	0.418
.80/.80	.60/.70	229.1	76.6	0.140	0	0.486
.80/.90	.60/.75	281.1	93.7	0.774	0	0.116
Enrichment Design						
.80/.80	.60/.60					
.80/.80	.60/.75					
.80/.80	.60/.70					
.80/.90	.60/.75					
Enrichment Design – Hierarchical Borrowing						
.80/.80	.60/.60					
.80/.80	.60/.75					
.80/.80	.60/.70					
.80/.90	.60/.75					

Enrichment Design

- Do an interim analysis when 100 subjects are enrolled (use LM model)
- Additional analyses every 12 weeks (cap of 300)
  - Stop the low Triponen Group if the probability it meets CSD (7.5%) is < 0.10
  - Stop entire trial if High Triponen Group has probability meets CSD < 0.10
- Success at the end of the trial is
  - Statistical superiority (5%) on “All” subjects
  - Statistical Superiority (5%) on “High” subjects

Results

Low	High	Mean N	High N	Pr(Win)	Pr(Enrich)	Pr(Futility)
.80/.80	.60/.60	191.8	63.6	0.048	0	0.694
.80/.80	.60/.75	237.9	79.3	0.224	0	0.418
.80/.80	.60/.70	229.1	76.6	0.140	0	0.486
.80/.90	.60/.75	281.1	93.7	0.774	0	0.116
Enrichment Design						
.80/.80	.60/.60	233.1	102.0	0.064/0.018	0.612	0.558
.80/.80	.60/.75	290.0	155.3	0.636/0.162	0.630	0.080
.80/.80	.60/.70	280.3	151.4	0.398/0.120	0.638	0.166
.80/.90	.60/.75	293.7	115.4	0.832/0.018	0.182	0.056
Enrichment Design – Hierarchical Borrowing						
.80/.80	.60/.60					
.80/.80	.60/.75					
.80/.80	.60/.70					
.80/.90	.60/.75					

Enrichment Design + Borrow

- Add in a hierarchical model for the treatment effects in each group

$$\log\left(\frac{\pi_g}{1-\pi_g}\right) \sim N\left(\mu, \tau^2\right)$$

$$[\mu] \sim N(0,10) \qquad \left[\tau^2\right] \sim IG(0.1, 0.1)$$

Results

Low	High	Mean N	High N	Pr(Win)	Pr(Enrich)	Pr(Futility)
.80/.80	.60/.60	191.8	63.6	0.048	0	0.694
.80/.80	.60/.75	237.9	79.3	0.224	0	0.418
.80/.80	.60/.70	229.1	76.6	0.140	0	0.486
.80/.90	.60/.75	281.1	93.7	0.774	0	0.116
Enrichment Design						
.80/.80	.60/.60	233.1	102.0	0.064/0.018	0.612	0.558
.80/.80	.60/.75	290.0	155.3	0.636/0.162	0.630	0.080
.80/.80	.60/.70	280.3	151.4	0.398/0.120	0.638	0.166
.80/.90	.60/.75	293.7	115.4	0.832/0.018	0.182	0.056
Enrichment Design – Hierarchical Borrowing						
.80/.80	.60/.60	207.9	98.1	0.042/0.012	0.812	0.678
.80/.80	.60/.75	273.7	134.6	0.552/0.104	0.600	0.180
.80/.80	.60/.70	252.7	123.5	0.262/0.052	0.674	0.350
.80/.90	.60/.75	295.0	116.7	0.846/0.020	0.153	0.040