Simulation report Supplementary Material: Sensitivity analyses

Tailored Interventions Guided by Endotypic Responses in Sepsis (TIGERS)

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Version 1-0

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1 Version history

Version	Date	Description	Authors	Software
V1-0	09/07/2025	Simulation results for the grant application	Anais Charles-Nelson Dr Elizabeth Ryan	R version 4.4.3 (2025-02-28 ucrt) INLA_24.12.11 built 2024-12-11 19:58:26 UTC

Table of contents

List of figures

List of tables

2 Scope of the report

Here we present the results of some sensitivity analyses that were performed for the simulation study for the TIGERS platform trial, where we vary:

1. The distribution of the primary endpoint
2. The recruitment rates
3. The proportion of SRS 1: SRS 2 patients

We summarise these assumptions below.

2.1 Distribution of the primary endpoint

2.1.1 Main assumption

category	Organ support free days	P control SRS 1	P control SRS 2
1	-1	0.2258	0.1757
2	0	0.0920	0.0622
3	1	0.0099	0.0076
4	2	0.0060	0.0096
5	3	0.0101	0.0060
6	4	0.0059	0.0101
7	5	0.0083	0.0087
8	6	0.0041	0.0116
9	7	0.0073	0.0144
10	8	0.0060	0.0096
11	9	0.0112	0.0054
12	10	0.0071	0.0054
13	11	0.0062	0.0160
14	12	0.0265	0.0067
15	13	0.0130	0.0094
16	14	0.0083	0.0103
17	15	0.0121	0.0257
18	16	0.0125	0.0122
19	17	0.0281	0.0212
20	18	0.0140	0.0396
21	19	0.0251	0.0190
22	20	0.0309	0.0386
23	21	0.0268	0.0343
24	22	0.0345	0.0407
25	23	0.0319	0.0406
26	24	0.0372	0.0517
27	25	0.0996	0.0904
28	26	0.1073	0.0874
29	27	0.0643	0.0773
30	28	0.0280	0.0526

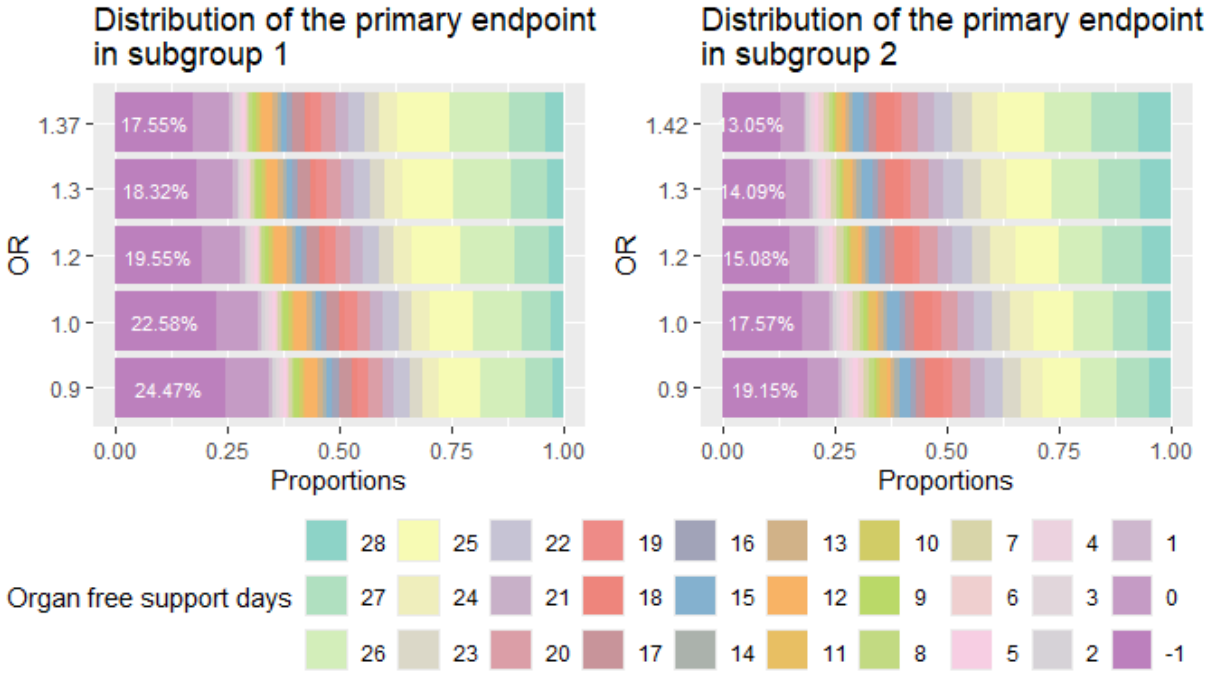

FIGURE 1: DISTRIBUTION OF THE PRIMARY ENDPOINT BY SRS GROUP FOR DIFFERENT ASSUMED TREATMENT EFFECT SIZES

2.1.2 Sensitivity analysis 1

The first sensitivity analysis assumed a higher mortality rate in the SRS1 phenotype.

category	Organ support free days	P control SRS 1	P control SRS 2
1	-1	**0.2758**	0.1757
2	0	0.0903	0.0622
3	1	0.0082	0.0076
4	2	0.0043	0.0096
5	3	0.0084	0.0060
6	4	0.0042	0.0101
7	5	0.0066	0.0087
8	6	0.0024	0.0116
9	7	0.0056	0.0144
10	8	0.0043	0.0096
11	9	0.0095	0.0054
12	10	0.0054	0.0054
13	11	0.0045	0.0160
14	12	0.0248	0.0067
15	13	0.0113	0.0094
16	14	0.0066	0.0103
17	15	0.0104	0.0257
18	16	0.0108	0.0122
19	17	0.0264	0.0212
20	18	0.0123	0.0396
21	19	0.0234	0.0190
22	20	0.0292	0.0386
23	21	0.0251	0.0343
24	22	0.0328	0.0407
25	23	0.0302	0.0406
26	24	0.0355	0.0517
27	25	0.0979	0.0904
28	26	0.1056	0.0874
29	27	0.0624	0.0773
30	28	0.0258	0.0527

2.1.3 Sensitivity analysis 2

The second sensitivity analysis assumed a higher mortality rate in the SRS2 phenotype.

category	Organ support free days	P control SRS 1	P control SRS 2
1	-1	0.2258	**0.2257**
2	0	0.0920	0.0605
3	1	0.0099	0.0059
4	2	0.0060	0.0079
5	3	0.0101	0.0043
6	4	0.0059	0.0084
7	5	0.0083	0.0070
8	6	0.0041	0.0099
9	7	0.0073	0.0127
10	8	0.0060	0.0079
11	9	0.0112	0.0037
12	10	0.0071	0.0037
13	11	0.0062	0.0143
14	12	0.0265	0.0050
15	13	0.0130	0.0077
16	14	0.0083	0.0086
17	15	0.0121	0.0240
18	16	0.0125	0.0105
19	17	0.0281	0.0195
20	18	0.0140	0.0379
21	19	0.0251	0.0173
22	20	0.0309	0.0369
23	21	0.0268	0.0326
24	22	0.0345	0.0390
25	23	0.0319	0.0389
26	24	0.0372	0.0500
27	25	0.0996	0.0887
28	26	0.1073	0.0857
29	27	0.0643	0.0756
30	28	0.0280	0.0509

2.1.4 Sensitivity Analysis 3

In the third sensitivity analysis, the tail top probabilities (-1, 0 categories) are kept the same as in the main analysis and the probabilities of the other categories (1-28) are evenly distributed.

category	Organ support free days	P control SRS 1	P control SRS 2
1	-1	0.2258	0.1757
2	0	0.0920	0.0622
3	1	0.0244	0.0272
4	2	0.0244	0.0272
5	3	0.0244	0.0272
6	4	0.0244	0.0272
7	5	0.0244	0.0272
8	6	0.0244	0.0272
9	7	0.0244	0.0272
10	8	0.0244	0.0272
11	9	0.0244	0.0272
12	10	0.0244	0.0272
13	11	0.0244	0.0272
14	12	0.0244	0.0272
15	13	0.0244	0.0272
16	14	0.0244	0.0272
17	15	0.0244	0.0272
18	16	0.0244	0.0272
19	17	0.0244	0.0272
20	18	0.0244	0.0272
21	19	0.0244	0.0272
22	20	0.0244	0.0272
23	21	0.0244	0.0272
24	22	0.0244	0.0272
25	23	0.0244	0.0272
26	24	0.0244	0.0272
27	25	0.0244	0.0272
28	26	0.0242	0.0272
29	27	0.0240	0.0274
30	28	0.0240	0.0275

2.2 Recruitment rate

2.2.1 Main assumption

We assume a total of 60 sites with a recruitment rate of 1.5 patients per site and that it takes 21 months to get all 60 sites up and running. The UK will contribute 40 sites and Australia will contribute 20 sites.

Month	Number of sites	Number patients per site	Number of patients per month total	Cumulative number of patients
1	1	1.5	1.5	1.5
2	2	1.5	3.0	4.5
3	3	1.5	4.5	9.0
4	5	1.5	7.5	16.5
5	5	1.5	7.5	24.0
6	10	1.5	15.0	39.0
7	10	1.5	15.0	54.0
8	15	1.5	22.5	76.5
9	15	1.5	22.5	99.0
10	20	1.5	30.0	129.0
11	20	1.5	30.0	159.0
12	25	1.5	37.5	196.5
13	25	1.5	37.5	234.0
14	30	1.5	45.0	279.0
15	30	1.5	45.0	324.0
16	35	1.5	52.5	376.5
17	40	1.5	60.0	436.5
18	45	1.5	67.5	504.0
19	50	1.5	75.0	579.0
20	55	1.5	82.5	661.5
21	60	1.5	90.0	751.5
22	60	1.5	90.0	841.5
23	60	1.5	90.0	931.5
24	60	1.5	90.0	1,021.5
25	60	1.5	90.0	1,111.5
26	60	1.5	90.0	1,201.5
27	60	1.5	90.0	1,291.5
28	60	1.5	90.0	1,381.5
29	60	1.5	90.0	1,471.5
30	60	1.5	90.0	1,561.5
31	60	1.5	90.0	1,651.5
32	60	1.5	90.0	1,741.5
33	60	1.5	90.0	1,831.5
34	60	1.5	90.0	1,921.5
35	60	1.5	90.0	2,011.5
36	60	1.5	90.0	2,101.5
37	60	1.5	90.0	2,191.5
38	60	1.5	90.0	2,281.5
39	60	1.5	90.0	2,371.5
40	60	1.5	90.0	2,461.5
41	60	1.5	90.0	2,551.5
42	60	1.5	90.0	2,641.5

2.2.2 Sensitivity analysis 1

In the first sensitivity analysis, we assumed a smaller number of patients per site.

Month	Number of sites	Number patients per site	Number of patients per month total	Cumulative number of patients
1	1	1.25	1.25	1.25
2	2	1.25	2.50	3.75
3	3	1.25	3.75	7.50
4	5	1.25	6.25	13.75
5	5	1.25	6.25	20.00
6	10	1.25	12.50	32.50
7	10	1.25	12.50	45.00
8	15	1.25	18.75	63.75
9	15	1.25	18.75	82.50
10	20	1.25	25.00	107.50
11	20	1.25	25.00	132.50
12	25	1.25	31.25	163.75
13	25	1.25	31.25	195.00
14	30	1.25	37.50	232.50
15	30	1.25	37.50	270.00
16	35	1.25	43.75	313.75
17	40	1.25	50.00	363.75
18	45	1.25	56.25	420.00
19	50	1.25	62.50	482.50
20	55	1.25	68.75	551.25
21	60	1.25	75.00	626.25
22	60	1.25	75.00	701.25
23	60	1.25	75.00	776.25
24	60	1.25	75.00	851.25
25	60	1.25	75.00	926.25
26	60	1.25	75.00	1,001.25
27	60	1.25	75.00	1,076.25
28	60	1.25	75.00	1,151.25
29	60	1.25	75.00	1,226.25
30	60	1.25	75.00	1,301.25
31	60	1.25	75.00	1,376.25
32	60	1.25	75.00	1,451.25
33	60	1.25	75.00	1,526.25
34	60	1.25	75.00	1,601.25
35	60	1.25	75.00	1,676.25
36	60	1.25	75.00	1,751.25
37	60	1.25	75.00	1,826.25
38	60	1.25	75.00	1,901.25
39	60	1.25	75.00	1,976.25
40	60	1.25	75.00	2,051.25
41	60	1.25	75.00	2,126.25
42	60	1.25	75.00	2,201.25

2.2.3 Sensitivity analysis 2

In the second sensitivity analysis, we assumed a slower initial recruitment rate (fewer per site, and that it took longer to reach 60 sites).

Month	Number of sites	Number patients per site	Number of patients per month total	Cumulative number of patients
1	1	1.00	1.00	1.00
2	2	1.00	2.00	3.00
3	3	1.00	3.00	6.00
4	4	1.00	4.00	10.00
5	5	1.00	5.00	15.00
6	6	1.00	6.00	21.00
7	8	1.25	10.00	31.00
8	10	1.25	12.50	43.50
9	12	1.25	15.00	58.50
10	15	1.25	18.75	77.25
11	18	1.25	22.50	99.75
12	21	1.25	26.25	126.00
13	25	1.50	37.50	163.50
14	28	1.50	42.00	205.50
15	31	1.50	46.50	252.00
16	34	1.50	51.00	303.00
17	37	1.50	55.50	358.50
18	40	1.50	60.00	418.50
19	43	1.50	64.50	483.00
20	46	1.50	69.00	552.00
21	49	1.50	73.50	625.50
22	52	1.50	78.00	703.50
23	55	1.50	82.50	786.00
24	58	1.50	87.00	873.00
25	60	1.50	90.00	963.00
26	60	1.50	90.00	1,053.00
27	60	1.50	90.00	1,143.00
28	60	1.50	90.00	1,233.00
29	60	1.50	90.00	1,323.00
30	60	1.50	90.00	1,413.00
31	60	1.50	90.00	1,503.00
32	60	1.50	90.00	1,593.00
33	60	1.50	90.00	1,683.00
34	60	1.50	90.00	1,773.00
35	60	1.50	90.00	1,863.00
36	60	1.50	90.00	1,953.00
37	60	1.50	90.00	2,043.00
38	60	1.50	90.00	2,133.00
39	60	1.50	90.00	2,223.00
40	60	1.50	90.00	2,313.00
41	60	1.50	90.00	2,403.00
42	60	1.50	90.00	2,493.00

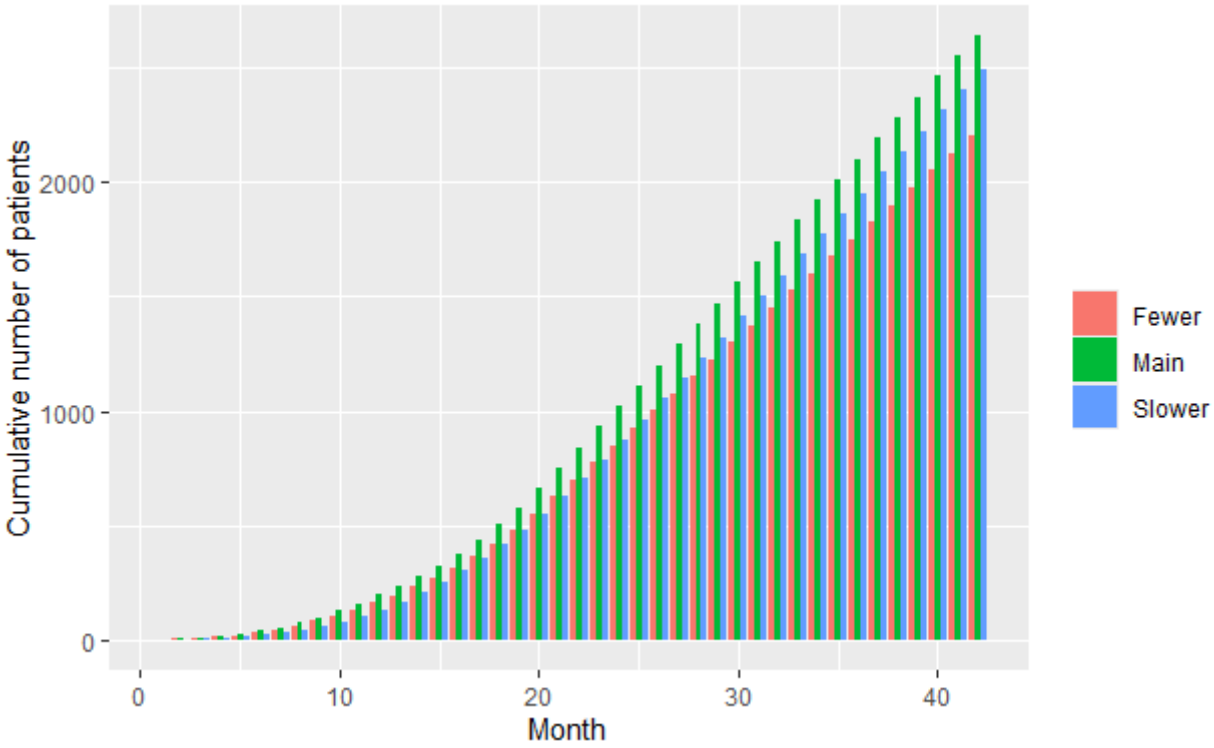

FIGURE 2: CUMULATIVE NUMBER OF PATIENTS RECRUITED ACROSS DIFFERENT SCENARIOS

2.3 Other parameters

Parameter	Main	Sensitivity analysis
Treatment effect size (POR for Anti-IL6, POR for anti-TNF alpha)	(1.37,1.37) (SRS 1; 5% absolute decrease in mortality; "power" scenario) (1.42,1.42) (SRS 2; 4.5% absolute decrease in mortality; "power" scenario) (1,1) (type I error)	POR for treatment 1 = power OR POR for treatment 2: 0.9, 1, 1.2, 1.3, 1.4*
Split between phenotype	40% (SRS 1) vs 60% (SRS 2)	**30% (SRS 1) vs 70% (SRS 2)** **50% (SRS 1) vs 50% (SRS 2)**

*These results are provided in the main report; a POR=1.4 was only explored for SRS1

We present the results of varying the SRS proportions in this report.

Alternative interim analysis schedules were also explored where we varied the timing of the first interim analysis, the decisions that could be made at the first interim analyses, and the timing of subsequent interim analyses (results not presented here).

3 Simulation results

3.1 Sensitivity analyses

3.1.1 Different split between SRS1 and SRS2

Here we explore different SRS 1: SRS 2 ratios in the study population. We only investigated these for the type I error and power scenarios (for both binding and non-binding futility)

3.1.1.1 Non-binding futility

3.1.1.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 1: VARYING SRS RATIO: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	885/ 992 (89%)	107/ 992 (11%)	894/ 984 (91%)	90/ 984 (9.1%)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	885/ 982 (90%)	97/ 982 (9.9%)	883/ 977 (90%)	94/ 977 (9.6%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	276/ 990 (28%)	714/ 990 (72%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	225/ 980 (23%)	755/ 980 (77%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7			157/ 961 (16%)	804/ 961 (84%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5			165/ 966 (17%)	801/ 966 (83%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	890/ 992 (90%)	102/ 992 (10%)	892/ 984 (91%)	92/ 984 (9.3%)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	874/ 982 (89%)	108/ 982 (11%)	883/ 977 (90%)	94/ 977 (9.6%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	279/ 990 (28%)	711/ 990 (72%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	225/ 980 (23%)	755/ 980 (77%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7			162/ 961 (17%)	799/ 961 (83%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5			167/ 966 (17%)	799/ 966 (83%)

[1]n/ N (%)

3.1.1.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 2: VARYING SRS RATIO: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 984[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Max recruitment period	859/ 992 (87%)	
						Reached sample size cap		866/ 984 (88%)
						Superiority at interim analysis	133/ 992 (13%)	118/ 984 (12%)
						Sample size	242 (48) 250 [241-258] (108-359)	377 (68) 400 [400-400] (143-400)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		
						Max recruitment period	748/ 982 (76%)	38/ 977 (3.9%)
						Reached sample size cap	90/ 982 (9.2%)	806/ 977 (82%)
						Superiority at interim analysis	144/ 982 (15%)	133/ 977 (14%)
						Sample size	389 (86) 417 [406-428] (127-450)	371 (77) 400 [400-400] (130-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Max recruitment period	274/ 990 (28%)	
						Superiority at interim analysis	716/ 990 (72%)	
						Sample size	186 (74) 167 [118-252] (103-363)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		
						Max recruitment period	68/ 980 (6.9%)	

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 984[1]
						Reached sample size cap	112/ 980 (11%)	
						Superiority at interim analysis	800/ 980 (82%)	
						Sample size	250 (120) 166 [147-390] (127-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Reached sample size cap		161/ 961 (17%)
						Superiority at interim analysis		800/ 961 (83%)
						Sample size		242 (100) 173 [162-352] (139-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		
						Max recruitment period		1/ 966 (0.1%)
						Reached sample size cap		165/ 966 (17%)
						Superiority at interim analysis		800/ 966 (83%)
						Sample size		227 (101) 157 [145-296] (126-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Max recruitment period	851/ 992 (86%)	
						Reached sample size cap		850/ 984 (86%)
						Superiority at interim analysis	141/ 992 (14%)	134/ 984 (14%)
						Sample size	241 (48) 250 [241-257](103-360)	374 (70) 400 [400-400](149-400)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 984[1]
						Max recruitment period	742/ 982 (76%)	30/ 977 (3.1%)
						Reached sample size cap	93/ 982 (9.5%)	809/ 977 (83%)
						Superiority at interim analysis	147/ 982 (15%)	138/ 977 (14%)
						Sample size	387 (88) 417 [405-428](120-450)	371 (77) 400 [400-400](127-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Max recruitment period	260/ 990 (26%)	
						Superiority at interim analysis	730/ 990 (74%)	
						Sample size	184 (73) 167 [118-248](100-357)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		
						Max recruitment period	67/ 980 (6.8%)	
						Reached sample size cap	101/ 980 (10%)	
						Superiority at interim analysis	812/ 980 (83%)	
						Sample size	245 (118) 161 [147-359](120-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Stopping reason		
						Reached sample size cap		161/ 961 (17%)
						Superiority at interim analysis		800/ 961 (83%)
						Sample size		238 (99) 171 [162-346](141-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Stopping reason		

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 984[1]
						Max recruitment period		2/ 966 (0.2%)
						Reached sample size cap		186/ 966 (19%)
						Superiority at interim analysis		778/ 966 (81%)
						Sample size		228 (103) 157 [145-309](125-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 3: VARYING SRS RATIO: SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 1,000[1]	Treatment 1 N = 1,000[1]	Treatment 2 N = 1,000[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.3 vs 0.7	613 (180) 682 [386-784] [324-883]	186 (74) 167 [118-252] [103-363]	184 (73) 167 [118-248] [100-357]
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.5 vs 0.5	825 (313) 753 [478-1,074] [389-1,399]	250 (120) 166 [147-390] [127-450]	245 (118) 161 [147-359] [120-450]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.3 vs 0.7	775 (82) 790 [770-807] [333-883]	242 (48) 250 [241-258] [108-359]	241 (48) 250 [241-257] [103-360]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.5 vs 0.5	1,247 (179) 1,307 [1,264-1,336] [389-1,423]	389 (86) 417 [406-428] [127-450]	387 (88) 417 [405-428] [120-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.5 vs 0.5	757 (267) 731 [473-976] [407-1,277]	227 (101) 157 [145-296] [126-400]	228 (103) 157 [145-309] [125-400]
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.3 vs 0.7	792 (261) 867 [522-980] [449-1,282]	242 (100) 173 [162-352] [139-400]	238 (99) 171 [162-346] [141-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.5 vs 0.5	1,191 (164) 1,263 [1,248-1,268] [407-1,279]	371 (77) 400 [400-400] [130-400]	371 (77) 400 [400-400] [127-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.3 vs 0.7	1,206 (133) 1,265 [1,258-1,269] [479-1,282]	377 (68) 400 [400-400] [143-400]	374 (70) 400 [400-400] [149-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.1.1.3 Timing of the trial analyses

TABLE 4: VARYING SRS RATIO: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 992[1]	SRS 2 N = 984[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time first interim analysis (months)	20.42 (0.56) 20.42 [20.05-20.80] (18.60-22.37)	14.86 (0.48) 14.86 [14.53-15.19] (13.50-16.37)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time final analysis for treatment 1 (months)	42.1 (5.0) 44.0 [44.0-44.0] (26.0-44.0)	33.5 (4.0) 35.0 [34.0-36.0] (20.6-41.0)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time first interim analysis (months)	16.94 (0.52) 16.95 [16.58-17.30] (15.31-18.60)	16.89 (0.55) 16.92 [16.51-17.24] (15.16-18.71)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time final analysis for treatment 1 (months)	41 (6) 44 [44-44] (23-44)	40.5 (6.0) 43.0 [42.0-44.0] (22.4-44.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time first interim analysis (months)	20.42 (0.57) 20.42 [20.05-20.81] (18.60-22.37)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 – peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time final analysis for treatment 1 (months)	34.2 (7.2) 33.1 [27.5-44.0] (26.0-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time first interim analysis (months)	16.94 (0.52) 16.95 [16.59-17.30] (15.31-18.60)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time final analysis for treatment 1 (months)	30 (7) 25 [24-36] (22-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time first interim analysis (months)		14.86 (0.47) 14.86 [14.53-15.19] (13.50-16.37)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.3 vs 0.7	Time final analysis for treatment 1 (months)		25.3 (4.6) 22.3 [21.7-28.1] (20.5-36.0)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 992[1]	SRS 2 N = 984[1]
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time first interim analysis (months)		16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.5 vs 0.5	Time final analysis for treatment 1 (months)		28.7 (6.2) 24.7 [23.9-30.9] (22.3-44.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.1.2 Binding futility

3.1.1.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 5: VARYING SRS RATIO: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.3 vs 0.7	892/ 989 (90%)	97/ 989 (9.8%)	918/ 985 (93%)	67/ 985 (6.8%)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.5 vs 0.5	883/ 979 (90%)	96/ 979 (9.8%)	897/ 982 (91%)	85/ 982 (8.7%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.3 vs 0.7	317/ 991 (32%)	674/ 991 (68%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.5 vs 0.5	267/ 981 (27%)	714/ 981 (73%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.3 vs 0.7			202/ 962 (21%)	760/ 962 (79%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.5 vs 0.5			196/ 967 (20%)	771/ 967 (80%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.3 vs 0.7	892/ 989 (90%)	97/ 989 (9.8%)	906/ 985 (92%)	79/ 985 (8.0%)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.5 vs 0.5	881/ 979 (90%)	98/ 979 (10%)	899/ 982 (92%)	83/ 982 (8.5%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.3 vs 0.7	314/ 991 (32%)	677/ 991 (68%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut=0.8	FALSE	0.5 vs 0.5	249/ 981 (25%)	732/ 981 (75%)		

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7			199/ 962 (21%)	763/ 962 (79%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5			223/ 967 (23%)	744/ 967 (77%)

[1]n/ N (%)

3.1.1.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 6: VARYING SRS RATIO: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 985[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis	585/ 989 (59%)	543/ 985 (55%)
						Max recruitment period	277/ 989 (28%)	
						Reached sample size cap		347/ 985 (35%)
						Superiority at interim analysis	127/ 989 (13%)	95/ 985 (9.6%)
						Sample size	168 (99) 133 [68-251] (59-395)	242 (139) 231 [74-400] (62-400)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis	617/ 979 (63%)	582/ 982 (59%)
						Max recruitment period	77/ 979 (7.9%)	2/ 982 (0.2%)
						Reached sample size cap	147/ 979 (15%)	277/ 982 (28%)
						Superiority at interim analysis	138/ 979 (14%)	121/ 982 (12%)
						Sample size	229 (148) 181 [71-406] (60-450)	218 (137) 169 [70-400] (59-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis	118/ 991 (12%)	
						Max recruitment period	179/ 991 (18%)	
						Superiority at interim analysis	694/ 991 (70%)	

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 985[1]
						Sample size	169 (79) 124 [116-231] (60-374)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis	112/ 981 (11%)	
						Max recruitment period	25/ 981 (2.5%)	
						Reached sample size cap	94/ 981 (9.6%)	
						Superiority at interim analysis	750/ 981 (76%)	
						Sample size	218 (118) 154 [144-287] (62-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis		60/ 962 (6.2%)
						Reached sample size cap		120/ 962 (12%)
						Superiority at interim analysis		782/ 962 (81%)
						Sample size		224 (100) 170 [160-332] (65-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis		60/ 967 (6.2%)
						Reached sample size cap		136/ 967 (14%)
						Superiority at interim analysis		771/ 967 (80%)
						Sample size		214 (100) 154 [143-285] (60-400)
Treatment2								

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 985[1]
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis	554/ 989 (56%)	539/ 985 (55%)
						Max recruitment period	297/ 989 (30%)	
						Reached sample size cap		338/ 985 (34%)
						Superiority at interim analysis	138/ 989 (14%)	108/ 985 (11%)
						Sample size	177 (100) 152 [69-256](59-377)	248 (137) 256 [77-400](63-400)
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis	588/ 979 (60%)	580/ 982 (59%)
						Max recruitment period	74/ 979 (7.6%)	1/ 982 (0.1%)
						Reached sample size cap	186/ 979 (19%)	282/ 982 (29%)
						Superiority at interim analysis	131/ 979 (13%)	119/ 982 (12%)
						Sample size	240 (152) 196 [72-417](61-450)	221 (137) 187 [70-400](60-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis	115/ 991 (12%)	
						Max recruitment period	169/ 991 (17%)	
						Superiority at interim analysis	707/ 991 (71%)	
						Sample size	170 (79) 124 [116-228](59-400)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis	93/ 981 (9.5%)	

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 985[1]
						Max recruitment period	17/ 981 (1.7%)	
						Reached sample size cap	80/ 981 (8.2%)	
						Superiority at interim analysis	791/ 981 (81%)	
						Sample size	219 (113) 155 [144-286](63-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Stopping reason		
						Futility at interim analysis		68/ 962 (7.1%)
						Reached sample size cap		115/ 962 (12%)
						Superiority at interim analysis		779/ 962 (81%)
						Sample size		220 (98) 168 [160-292](64-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Stopping reason		
						Futility at interim analysis		96/ 967 (9.9%)
						Max recruitment period		1/ 967 (0.1%)
						Reached sample size cap		138/ 967 (14%)
						Superiority at interim analysis		732/ 967 (76%)
						Sample size		205 (103) 152 [142-276](60-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 7: VARYING SRS RATIO: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 1,000[1]	Treatment 1 N = 1,000[1]	Treatment 2 N = 1,000[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.3 vs 0.7	570 (185) 544 [378-765] [192-883]	169 (79) 124 [116-231] [60-374]	170 (79) 124 [116-228] [59-400]
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.5 vs 0.5	737 (288) 723 [467-1,005] [202-1,368]	218 (118) 154 [144-287] [62-450]	219 (113) 155 [144-286] [63-450]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.3 vs 0.7	590 (227) 704 [373-789] [192-872]	168 (99) 133 [68-251] [59-395]	177 (100) 152 [69-256] [59-377]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.5 vs 0.5	808 (356) 973 [470-1,072] [194-1,375]	229 (148) 181 [71-406] [60-450]	240 (152) 196 [72-417] [61-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.5 vs 0.5	703 (253) 712 [466-963] [198-1,273]	214 (100) 154 [143-285] [60-400]	205 (103) 152 [142-276] [60-400]
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.3 vs 0.7	738 (249) 811 [516-921] [209-1,273]	224 (100) 170 [160-332] [65-400]	220 (98) 168 [160-292] [64-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.5 vs 0.5	754 (330) 874 [463-978] [192-1,276]	218 (137) 169 [70-400] [59-400]	221 (137) 187 [70-400] [60-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.3 vs 0.7	837 (319) 888 [537-1,016] [201-1,279]	242 (139) 231 [74-400] [62-400]	248 (137) 256 [77-400] [63-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.1.2.3 Timing of the trial

TABLE 8: VARYING SRS RATIO: TIME OF FIRST INTERIM ANALYSIS AND TIME OF THE FINAL ANALYSIS (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 989[1]	SRS 2 N = 985[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time first interim analysis (months)	20.42 (0.56) 20.42 [20.05-20.79] (18.60-22.37)	14.86 (0.48) 14.86 [14.53-15.19] (13.50-16.37)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time final analysis for treatment 1 (months)	32 (9) 28 [22-44] (20-44)	24.7 (7.1) 22.6 [16.4-31.0] (14.7-37.0)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time first interim analysis (months)	16.94 (0.52) 16.95 [16.58-17.30] (15.31-18.60)	16.89 (0.55) 16.92 [16.51-17.24] (15.16-18.71)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time final analysis for treatment 1 (months)	28 (9) 24 [18-36] (16-44)	27 (9) 24 [18-35] (16-44)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time first interim analysis (months)	20.42 (0.57) 20.42 [20.04-20.81] (18.60-22.37)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time final analysis for treatment 1 (months)	32 (7) 28 [27-39] (20-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time first interim analysis (months)	16.94 (0.52) 16.95 [16.59-17.30] (15.31-18.60)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time final analysis for treatment 1 (months)	28 (7) 24 [24-30] (16-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time first interim analysis (months)		14.86 (0.47) 14.86 [14.53-15.19] (13.50-16.37)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.3 vs 0.7	Time final analysis for treatment 1 (months)		24.2 (4.5) 22.2 [21.6-27.8] (14.8-36.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time first interim analysis (months)		16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.5 vs 0.5	Time final analysis for treatment 1 (months)		27.5 (5.9) 24.4 [23.7-30.1] (16.5-44.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2 Different distribution of the primary endpoint

3.1.2.1 Higher mortality in SRS 1

3.1.2.1.1 Non-binding futility

3.1.2.1.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 9: MORTALITY HIGHER IN SRS1: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

						Subgroup 1		Subgroup 2	
Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	891/ 985 (90%)	94/ 985 (9.5%)	890/ 977 (91%)	87/ 977 (8.9%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	225/ 979 (23%)	754/ 979 (77%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			150/ 971 (15%)	821/ 971 (85%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	878/ 985 (89%)	107/ 985 (11%)	886/ 977 (91%)	91/ 977 (9.3%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	219/ 979 (22%)	760/ 979 (78%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			160/ 971 (16%)	811/ 971 (84%)

[1] n/ N (%)

3.1.2.1.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 10: MORTALITY HIGHER IN SRS1: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 985[1]	SRS 2 N = 977[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	818/ 985 (83%)	
						Reached sample size cap	31/ 985 (3.1%)	852/ 977 (87%)
						Superiority at interim analysis	136/ 985 (14%)	125/ 977 (13%)
						Sample size	321 (70) 333 [324-343] (121-450)	376 (69) 400 [400-400] (137-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	171/ 979 (17%)	
						Reached sample size cap	33/ 979 (3.4%)	
						Superiority at interim analysis	775/ 979 (79%)	
						Sample size	227 (105) 197 [135-325] (120-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		168/ 971 (17%)
						Superiority at interim analysis		803/ 971 (83%)
						Sample size		236 (100) 165 [154-326] (134-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 985[1]	SRS 2 N = 977[1]
						Max recruitment period	807/ 985 (82%)	
						Reached sample size cap	41/ 985 (4.2%)	847/ 977 (87%)
						Superiority at interim analysis	137/ 985 (14%)	130/ 977 (13%)
						Sample size	321 (70) 333 [323-344](118-450)	372 (75) 400 [400-400](137-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	146/ 979 (15%)	
						Reached sample size cap	25/ 979 (2.6%)	
						Superiority at interim analysis	808/ 979 (83%)	
						Sample size	215 (100) 147 [134-276](116-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		187/ 971 (19%)
						Superiority at interim analysis		784/ 971 (81%)
						Sample size		238 (101) 166 [154-331](137-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 11: MORTALITY HIGHER IN SRS1: SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 994[1]	Treatment 1 N = 994[1]	Treatment 2 N = 994[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	739 (257) 669 [440-1,033] [379-1,153]	227 (105) 197 [135-325] [120-450]	215 (100) 147 [134-276] [116-450]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,034 (107) 1,052 [1,032-1,072] [387-1,153]	321 (70) 333 [324-343] [121-450]	321 (70) 333 [323-344] [118-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	784 (265) 809 [498-986] [432-1,281]	236 (100) 165 [154-326] [134-400]	238 (101) 166 [154-331] [137-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,199 (159) 1,265 [1,258-1,269] [439-1,287]	376 (69) 400 [400-400] [137-400]	372 (75) 400 [400-400] [137-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.1.1.3 Timing of the trial analyses

TABLE 12: MORTALITY HIGHER IN SRS1:TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 985[1]	SRS 2 N = 977[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.43 (0.53) 18.45 [18.07-18.76] (16.55-20.05)	15.74 (0.50) 15.72 [15.39-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	41.8 (5.6) 44.0 [44.0-44.0] (24.0-44.0)	36.6 (4.7) 38.0 [38.0-39.0] (21.7-41.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.43 (0.53) 18.45 [18.07-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	32.0 (7.4) 30.8 [25.5-37.7] (23.6-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)		15.73 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		26.8 (5.3) 23.3 [22.6-29.4] (21.1-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2.1.2 Binding futility

3.1.2.1.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 13: MORTALITY HIGHER IN SRS1: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	898/ 984 (91%)	86/ 984 (8.7%)	902/ 977 (92%)	75/ 977 (7.7%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	252/ 978 (26%)	726/ 978 (74%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			198/ 972 (20%)	774/ 972 (80%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	891/ 984 (91%)	93/ 984 (9.5%)	895/ 977 (92%)	82/ 977 (8.4%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	257/ 978 (26%)	721/ 978 (74%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			212/ 972 (22%)	760/ 972 (78%)

[1]n/ N (%)

3.1.2.1.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 14: MORTALITY HIGHER IN SRS1: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 984[1]	SRS 2 N = 977[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	605/ 984 (61%)	566/ 977 (58%)
						Max recruitment period	171/ 984 (17%)	
						Reached sample size cap	70/ 984 (7.1%)	298/ 977 (31%)
						Superiority at interim analysis	138/ 984 (14%)	113/ 977 (12%)
						Sample size	207 (133) 159 [71-329] (58-450)	236 (138) 209 [73-400] (61-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	95/ 978 (9.7%)	
						Max recruitment period	98/ 978 (10%)	
						Reached sample size cap	32/ 978 (3.3%)	
						Superiority at interim analysis	753/ 978 (77%)	
						Sample size	206 (107) 142 [132-270] (58-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		70/ 972 (7.2%)
						Reached sample size cap		128/ 972 (13%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 984[1]	SRS 2 N = 977[1]
						Superiority at interim analysis		774/ 972 (80%)
						Sample size		219 (100) 162 [152-312] (61-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	563/ 984 (57%)	576/ 977 (59%)
						Max recruitment period	187/ 984 (19%)	
						Reached sample size cap	106/ 984 (11%)	280/ 977 (29%)
						Superiority at interim analysis	128/ 984 (13%)	121/ 977 (12%)
						Sample size	224 (139) 187 [73-346](59-450)	228 (136) 194 [73-400](61-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	103/ 978 (11%)	
						Max recruitment period	83/ 978 (8.5%)	
						Reached sample size cap	30/ 978 (3.1%)	
						Superiority at interim analysis	762/ 978 (78%)	
						Sample size	196 (102) 140 [132-249](61-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		78/ 972 (8.0%)
						Reached sample size cap		147/ 972 (15%)
						Superiority at interim analysis		747/ 972 (77%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 984[1]	SRS 2 N = 977[1]
						Sample size		221 (103) 163 [152-314](63-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 15: MORTALITY HIGHER IN SRS1: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 994[1]	Treatment 1 N = 994[1]	Treatment 2 N = 994[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	679 (252) 644 [431-877] [200-1,153]	206 (107) 142 [132-270] [58-450]	196 (102) 140 [132-249] [61-450]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	743 (315) 861 [431-1,038] [190-1,140]	207 (133) 159 [71-329] [58-450]	224 (139) 187 [73-346] [59-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	734 (252) 788 [493-968] [201-1,281]	219 (100) 162 [152-312] [61-400]	221 (103) 163 [152-314] [63-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	794 (323) 876 [495-990] [197-1,279]	236 (138) 209 [73-400] [61-400]	228 (136) 194 [73-400] [61-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.1.2.3 Timing of the trial analyses

TABLE 16: MORTALITY HIGHER IN SRS1: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 984[1]	SRS 2 N = 977[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.43 (0.53) 18.45 [18.07-18.76] (16.55-20.05)	15.74 (0.50) 15.72 [15.39-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (10) 26 [20-42] (18-44)	26 (8) 24 [17-33] (15-40)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.43 (0.53) 18.45 [18.07-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (7) 26 [25-33] (18-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)		15.73 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		25.6 (5.1) 23.1 [22.5-28.8] (15.6-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2.2 Higher mortality in SRS 2

3.1.2.2.1 Non-binding futility

3.1.2.2.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 17: MORTALITY HIGHER IN SRS2: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	889/ 993 (90%)	104/ 993 (10%)	886/ 952 (93%)	66/ 952 (6.9%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	238/ 990 (24%)	752/ 990 (76%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			150/ 935 (16%)	785/ 935 (84%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	875/ 993 (88%)	118/ 993 (12%)	871/ 952 (91%)	81/ 952 (8.5%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	215/ 990 (22%)	775/ 990 (78%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			179/ 935 (19%)	756/ 935 (81%)

[1]n/ N (%)

3.1.2.2.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 18: MORTALITY HIGHER IN SRS2: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 993[1]	SRS 2 N = 952[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	811/ 993 (82%)	
						Reached sample size cap	33/ 993 (3.3%)	852/ 952 (89%)
						Superiority at interim analysis	149/ 993 (15%)	100/ 952 (11%)
						Sample size	318 (73) 334 [324-343] (121-450)	379 (65) 400 [400-400] (135-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	182/ 990 (18%)	
						Reached sample size cap	34/ 990 (3.4%)	
						Superiority at interim analysis	774/ 990 (78%)	
						Sample size	223 (105) 188 [135-327] (114-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		182/ 935 (19%)
						Superiority at interim analysis		753/ 935 (81%)
						Sample size		238 (101) 166 [154-328] (134-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 993[1]	SRS 2 N = 952[1]
						Max recruitment period	802/ 993 (81%)	
						Reached sample size cap	31/ 993 (3.1%)	834/ 952 (88%)
						Superiority at interim analysis	160/ 993 (16%)	118/ 952 (12%)
						Sample size	317 (73) 333 [322-343](120-450)	376 (68) 400 [400-400](138-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	169/ 990 (17%)	
						Reached sample size cap	29/ 990 (2.9%)	
						Superiority at interim analysis	792/ 990 (80%)	
						Sample size	218 (104) 145 [134-313](116-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		182/ 935 (19%)
						Superiority at interim analysis		753/ 935 (81%)
						Sample size		238 (100) 166 [154-324](137-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 19: MORTALITY HIGHER IN SRS2:SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 999[1]	Treatment 1 N = 999[1]	Treatment 2 N = 999[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	735 (267) 659 [436-1,038] [368-1,160]	223 (105) 188 [135-327] [114-450]	218 (104) 145 [134-313] [116-450]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,025 (127) 1,052 [1,031-1,072] [396-1,160]	318 (73) 334 [324-343] [121-450]	317 (73) 333 [322-343] [120-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	789 (262) 810 [501-987] [432-1,278]	238 (101) 166 [154-328] [134-400]	238 (100) 166 [154-324] [137-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,210 (138) 1,265 [1,259-1,269] [439-1,283]	379 (65) 400 [400-400] [135-400]	376 (68) 400 [400-400] [138-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.2.1.3 Timing of the trial analyses

TABLE 20: MORTALITY HIGHER IN SRS2: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 993[1]	SRS 2 N = 952[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	15.73 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	41.6 (6.0) 44.0 [44.0-44.0] (23.6-44.0)	36.8 (4.4) 38.0 [38.0-39.0] (21.4-41.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.45 [18.06-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	31.8 (7.5) 30.2 [25.5-37.8] (23.6-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)		15.74 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		27.0 (5.4) 23.4 [22.6-29.5] (21.1-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2.2.2 Binding futility

3.1.2.2.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 21: MORTALITY HIGHER IN SRS2: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	900/ 993 (91%)	93/ 993 (9.4%)	896/ 950 (94%)	54/ 950 (5.7%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	281/ 989 (28%)	708/ 989 (72%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			190/ 935 (20%)	745/ 935 (80%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	891/ 993 (90%)	102/ 993 (10%)	872/ 950 (92%)	78/ 950 (8.2%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	253/ 989 (26%)	736/ 989 (74%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			215/ 935 (23%)	720/ 935 (77%)

[1]n/ N (%)

3.1.2.2.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 22: MORTALITY HIGHER IN SRS2: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 993[1]	SRS 2 N = 950[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	580/ 993 (58%)	586/ 950 (62%)
						Max recruitment period	189/ 993 (19%)	
						Reached sample size cap	78/ 993 (7.9%)	279/ 950 (29%)
						Superiority at interim analysis	146/ 993 (15%)	85/ 950 (8.9%)
						Sample size	212 (133) 170 [72-334] (58-450)	227 (139) 173 [72-400] (61-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	112/ 989 (11%)	
						Max recruitment period	97/ 989 (9.8%)	
						Reached sample size cap	38/ 989 (3.8%)	
						Superiority at interim analysis	742/ 989 (75%)	
						Sample size	200 (106) 140 [132-251] (58-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		85/ 935 (9.1%)
						Reached sample size cap		127/ 935 (14%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 993[1]	SRS 2 N = 950[1]
						Superiority at interim analysis		723/ 935 (77%)
						Sample size		216 (101) 162 [152-307] (61-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	582/ 993 (59%)	559/ 950 (59%)
						Max recruitment period	186/ 993 (19%)	
						Reached sample size cap	79/ 993 (8.0%)	282/ 950 (30%)
						Superiority at interim analysis	146/ 993 (15%)	109/ 950 (11%)
						Sample size	220 (133) 182 [80-338](59-450)	233 (137) 208 [73-400](62-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	101/ 989 (10%)	
						Max recruitment period	84/ 989 (8.5%)	
						Reached sample size cap	33/ 989 (3.3%)	
						Superiority at interim analysis	771/ 989 (78%)	
						Sample size	197 (104) 140 [132-249](60-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		76/ 935 (8.1%)
						Reached sample size cap		145/ 935 (16%)
						Superiority at interim analysis		714/ 935 (76%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 993[1]	SRS 2 N = 950[1]
						Sample size		222 (102) 163 [152-314](62-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 23: MORTALITY HIGHER IN SRS2: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 999[1]	Treatment 1 N = 999[1]	Treatment 2 N = 999[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	671 (256) 632 [430-888] [190-1,125]	200 (106) 140 [132-251] [58-450]	197 (104) 140 [132-249] [60-450]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	742 (310) 849 [432-1,036] [190-1,147]	212 (133) 170 [72-334] [58-450]	220 (133) 182 [80-338] [59-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	733 (247) 784 [495-964] [209-1,278]	216 (101) 162 [152-307] [61-400]	222 (102) 163 [152-314] [62-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	788 (324) 876 [497-988] [196-1,277]	227 (139) 173 [72-400] [61-400]	233 (137) 208 [73-400] [62-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.2.2.3 Timing of the trial analyses

TABLE 24: MORTALITY HIGHER IN SRS2: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 993[1]	SRS 2 N = 950[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	15.73 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (10) 26 [20-42] (18-44)	26 (8) 23 [17-33] (15-40)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.45 [18.06-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (7) 26 [25-32] (18-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)		15.74 (0.51) 15.72 [15.38-16.08] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		25.4 (5.2) 23.1 [22.5-28.8] (15.4-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2.3 Other categories equal

3.1.2.3.1 Non-binding futility

3.1.2.3.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 25: OTHER CATEGORIES EQUAL: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	914/ 998 (92%)	84/ 998 (8.4%)	903/ 994 (91%)	91/ 994 (9.2%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	226/ 998 (23%)	772/ 998 (77%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			129/ 991 (13%)	862/ 991 (87%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	896/ 998 (90%)	102/ 998 (10%)	896/ 994 (90%)	98/ 994 (9.9%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	230/ 998 (23%)	768/ 998 (77%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			157/ 991 (16%)	834/ 991 (84%)

[1]n/ N (%)

3.1.2.3.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 26: OTHER CATEGORIES EQUAL: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 998[1]	SRS 2 N = 994[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	835/ 998 (84%)	
						Reached sample size cap	35/ 998 (3.5%)	876/ 994 (88%)
						Superiority at interim analysis	128/ 998 (13%)	118/ 994 (12%)
						Sample size	323 (67) 334 [325-344] (121-450)	377 (68) 400 [400-400] (139-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	176/ 998 (18%)	
						Reached sample size cap	45/ 998 (4.5%)	
						Superiority at interim analysis	777/ 998 (78%)	
						Sample size	226 (108) 193 [134-327] (120-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		168/ 991 (17%)
						Superiority at interim analysis		823/ 991 (83%)
						Sample size		239 (100) 166 [154-327] (136-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 998[1]	SRS 2 N = 994[1]
						Max recruitment period	834/ 998 (84%)	
						Reached sample size cap	29/ 998 (2.9%)	879/ 994 (88%)
						Superiority at interim analysis	135/ 998 (14%)	115/ 994 (12%)
						Sample size	321 (69) 334 [323-344](121-450)	377 (68) 400 [400-400](136-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	170/ 998 (17%)	
						Reached sample size cap	29/ 998 (2.9%)	
						Superiority at interim analysis	799/ 998 (80%)	
						Sample size	218 (105) 145 [134-320](118-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		176/ 991 (18%)
						Superiority at interim analysis		815/ 991 (82%)
						Sample size		237 (100) 166 [154-325](136-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 27: OTHER CATEGORIES EQUAL: SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 1,000[1]	Treatment 1 N = 1,000[1]	Treatment 2 N = 1,000[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	743 (267) 667 [438-1,040] [381-1,118]	226 (108) 193 [134-327] [120-450]	218 (105) 145 [134-320] [118-450]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,039 (94) 1,053 [1,033-1,073] [391-1,160]	323 (67) 334 [325-344] [121-450]	321 (69) 334 [323-344] [121-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	789 (258) 813 [502-986] [433-1,282]	239 (100) 166 [154-327] [136-400]	237 (100) 166 [154-325] [136-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,206 (150) 1,265 [1,260-1,269] [433-1,287]	377 (68) 400 [400-400] [139-400]	377 (68) 400 [400-400] [136-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.3.1.3 Timing of the trial analyses

TABLE 28: OTHER CATEGORIES EQUAL: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 998[1]	SRS 2 N = 994[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	15.74 (0.50) 15.72 [15.38-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	42.1 (5.3) 44.0 [44.0-44.0] (24.1-44.0)	36.7 (4.6) 38.0 [38.0-39.0] (21.4-43.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	32.0 (7.6) 30.4 [25.5-38.0] (23.6-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)		15.74 (0.51) 15.72 [15.38-16.09] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		26.9 (5.2) 23.4 [22.7-29.3] (21.4-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.2.3.2 Binding futility

3.1.2.3.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 29: OTHER CATEGORIES EQUAL: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	927/ 998 (93%)	71/ 998 (7.1%)	912/ 993 (92%)	81/ 993 (8.2%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	280/ 997 (28%)	717/ 997 (72%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			180/ 993 (18%)	813/ 993 (82%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	910/ 998 (91%)	88/ 998 (8.8%)	912/ 993 (92%)	81/ 993 (8.2%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	269/ 997 (27%)	728/ 997 (73%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			196/ 993 (20%)	797/ 993 (80%)

[1]n/ N (%)

3.1.2.3.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 30: OTHER CATEGORIES EQUAL: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 998[1]	SRS 2 N = 993[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	618/ 998 (62%)	584/ 993 (59%)
						Max recruitment period	181/ 998 (18%)	
						Reached sample size cap	84/ 998 (8.4%)	297/ 993 (30%)
						Superiority at interim analysis	115/ 998 (12%)	112/ 993 (11%)
						Sample size	214 (135) 172 [71-335] (58-450)	229 (137) 198 [73-400] (62-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	111/ 997 (11%)	
						Max recruitment period	93/ 997 (9.3%)	
						Reached sample size cap	44/ 997 (4.4%)	
						Superiority at interim analysis	749/ 997 (75%)	
						Sample size	200 (108) 140 [132-249] (58-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		75/ 993 (7.6%)
						Reached sample size cap		127/ 993 (13%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 998[1]	SRS 2 N = 993[1]
						Superiority at interim analysis		791/ 993 (80%)
						Sample size		221 (100) 164 [152-313] (63-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	582/ 998 (58%)	581/ 993 (59%)
						Max recruitment period	194/ 998 (19%)	
						Reached sample size cap	94/ 998 (9.4%)	312/ 993 (31%)
						Superiority at interim analysis	128/ 998 (13%)	100/ 993 (10%)
						Sample size	225 (137) 188 [74-342](59-450)	235 (138) 207 [73-400](61-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	96/ 997 (9.6%)	
						Max recruitment period	101/ 997 (10%)	
						Reached sample size cap	33/ 997 (3.3%)	
						Superiority at interim analysis	767/ 997 (77%)	
						Sample size	199 (106) 140 [132-253](60-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		70/ 993 (7.0%)
						Reached sample size cap		133/ 993 (13%)
						Superiority at interim analysis		790/ 993 (80%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 998[1]	SRS 2 N = 993[1]
						Sample size		222 (100) 164 [152-311](61-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 31: OTHER CATEGORIES EQUAL: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 1,000[1]	Treatment 1 N = 1,000[1]	Treatment 2 N = 1,000[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	676 (261) 633 [429-973] [199-1,117]	200 (108) 140 [132-249] [58-450]	199 (106) 140 [132-253] [60-450]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	756 (311) 875 [434-1,038] [192-1,153]	214 (135) 172 [71-335] [58-450]	225 (137) 188 [74-342] [59-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	740 (244) 794 [495-961] [200-1,271]	221 (100) 164 [152-313] [63-400]	222 (100) 164 [152-311] [61-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	790 (334) 875 [492-996] [197-1,278]	229 (137) 198 [73-400] [62-400]	235 (138) 207 [73-400] [61-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.2.3.2.3 Timing of the trial analyses

TABLE 32: OTHER CATEGORIES EQUAL: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 998[1]	SRS 2 N = 993[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	15.74 (0.50) 15.72 [15.38-16.08] (14.13-17.66)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (10) 26 [20-42] (18-44)	26 (8) 23 [17-33] (15-40)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	18.42 (0.53) 18.44 [18.06-18.76] (16.55-20.05)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	30 (7) 26 [25-32] (18-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)		15.74 (0.51) 15.72 [15.38-16.09] (14.13-17.66)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		25.7 (5.1) 23.2 [22.5-28.8] (15.6-40.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.3 Different recruitment rate

3.1.3.1 Fewer numbers recruited per site

3.1.3.1.1 Non-binding futility

3.1.3.1.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 33: FEWER NUMBER PER SITE: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	868/ 986 (88%)	118/ 986 (12%)	887/ 980 (91%)	93/ 980 (9.5%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	259/ 990 (26%)	731/ 990 (74%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			165/ 969 (17%)	804/ 969 (83%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	864/ 986 (88%)	122/ 986 (12%)	883/ 980 (90%)	97/ 980 (9.9%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	261/ 990 (26%)	729/ 990 (74%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			170/ 969 (18%)	799/ 969 (82%)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
					[1]n/ N (%)				

3.1.3.1.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 34: FEWER NUMBER PER SITE: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 986[1]	SRS 2 N = 980[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	842/ 986 (85%)	38/ 980 (3.9%)
						Superiority at interim analysis	144/ 986 (15%)	131/ 980 (13%)
						Sample size	267 (56) 278 [268-287] (109-401)	371 (77) 400 [400-400] (130-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	237/ 990 (24%)	
						Superiority at interim analysis	753/ 990 (76%)	
						Sample size	197 (84) 172 [124-274] (104-415)	
						Reached sample size cap		811/ 980 (83%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period		1/ 969 (0.1%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 986[1]	SRS 2 N = 980[1]
						Reached sample size cap		165/ 969 (17%)
						Superiority at interim analysis		803/ 969 (83%)
						Sample size		227 (101) 157 [145-297] (126-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	836/ 986 (85%)	32/ 980 (3.3%)
						Superiority at interim analysis	150/ 986 (15%)	141/ 980 (14%)
						Sample size	265 (57) 278 [268-286](113-406)	371 (77) 400 [400-400](127-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	244/ 990 (25%)	
						Superiority at interim analysis	746/ 990 (75%)	
						Sample size	195 (85) 135 [123-273](109-391)	
						Reached sample size cap		807/ 980 (82%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period		2/ 969 (0.2%)
						Reached sample size cap		187/ 969 (19%)
						Superiority at interim analysis		780/ 969 (80%)
						Sample size		229 (103) 157 [145-311](125-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 35: FEWER NUMBER PER SITE: SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 997[1]	Treatment 1 N = 997[1]	Treatment 2 N = 997[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	651 (210) 700 [403-868] [339-969]	197 (84) 172 [124-274] [104-415]	195 (85) 135 [123-273] [109-391]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	856 (101) 877 [856-897] [356-974]	267 (56) 278 [268-287] [109-401]	265 (57) 278 [268-286] [113-406]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	758 (267) 732 [473-976] [407-1,277]	227 (101) 157 [145-297] [126-400]	229 (103) 157 [145-311] [125-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,191 (164) 1,263 [1,249-1,268] [407-1,278]	371 (77) 400 [400-400] [130-400]	371 (77) 400 [400-400] [127-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.3.1.1.3 Timing of the trial analyses

TABLE 36: FEWER NUMBER PER SITE: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 986[1]	SRS 2 N = 980[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	19.69 (0.55) 19.69 [19.32-20.05] (17.68-21.41)	16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	41.9 (5.4) 44.0 [44.0-44.0] (25.6-44.0)	40.5 (6.0) 43.0 [42.0-44.0] (22.4-44.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	19.69 (0.54) 19.69 [19.32-20.05] (17.68-21.41)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	33.1 (7.2) 31.8 [26.7-39.3] (25.2-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)		16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		28.7 (6.2) 24.7 [23.9-30.9] (22.3-44.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.3.1.2 Binding futility

3.1.3.1.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 37: FEWER NUMBER PER SITE: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	872/ 990 (88%)	118/ 990 (12%)	898/ 982 (91%)	84/ 982 (8.6%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	286/ 991 (29%)	705/ 991 (71%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			195/ 969 (20%)	774/ 969 (80%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	883/ 990 (89%)	107/ 990 (11%)	899/ 982 (92%)	83/ 982 (8.5%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	285/ 991 (29%)	706/ 991 (71%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			222/ 969 (23%)	747/ 969 (77%)

[1]n/ N (%)

3.1.3.1.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 38: FEWER NUMBER PER SITE: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 990[1]	SRS 2 N = 982[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	579/ 990 (58%)	589/ 982 (60%)
						Max recruitment period	257/ 990 (26%)	2/ 982 (0.2%)
						Superiority at interim analysis	154/ 990 (16%)	120/ 982 (12%)
						Sample size	183 (110) 147 [70-277] (60-422)	218 (137) 169 [70-400] (59-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	109/ 991 (11%)	
						Max recruitment period	161/ 991 (16%)	
						Superiority at interim analysis	721/ 991 (73%)	
						Sample size	180 (87) 130 [122-234] (60-412)	
						Reached sample size cap		271/ 982 (28%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		59/ 969 (6.1%)
						Reached sample size cap		139/ 969 (14%)
						Superiority at interim analysis		771/ 969 (80%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 990[1]	SRS 2 N = 982[1]
						Sample size		214 (101) 154 [143-285] (60-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	573/ 990 (58%)	576/ 982 (59%)
						Max recruitment period	273/ 990 (28%)	1/ 982 (0.1%)
						Superiority at interim analysis	144/ 990 (15%)	120/ 982 (12%)
						Sample size	190 (111) 161 [71-282](59-437)	221 (138) 187 [70-400](60-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	110/ 991 (11%)	
						Max recruitment period	151/ 991 (15%)	
						Superiority at interim analysis	730/ 991 (74%)	
						Sample size	178 (87) 129 [122-232](62-422)	
						Reached sample size cap		285/ 982 (29%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		95/ 969 (9.8%)
						Max recruitment period		1/ 969 (0.1%)
						Reached sample size cap		139/ 969 (14%)
						Superiority at interim analysis		734/ 969 (76%)
						Sample size		206 (103) 152 [142-276](60-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 39: FEWER NUMBER PER SITE: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 998[1]	Treatment 1 N = 998[1]	Treatment 2 N = 998[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	603 (207) 567 [396-833] [198-966]	180 (87) 130 [122-234] [60-412]	178 (87) 129 [122-232] [62-422]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	639 (253) 739 [395-872] [188-966]	183 (110) 147 [70-277] [60-422]	190 (111) 161 [71-282] [59-437]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	704 (254) 712 [466-963] [198-1,273]	214 (101) 154 [143-285] [60-400]	206 (103) 152 [142-276] [60-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	754 (330) 874 [463-977] [192-1,276]	218 (137) 169 [70-400] [59-400]	221 (138) 187 [70-400] [60-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.3.1.2.3 Timing of the trial analyses

TABLE 40: FEWER NUMBER PER SITE: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 990[1]	SRS 2 N = 982[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	19.69 (0.54) 19.69 [19.32-20.05] (17.68-21.41)	16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	31 (9) 27 [21-44] (19-44)	27 (9) 24 [18-35] (16-44)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	19.68 (0.55) 19.69 [19.31-20.05] (17.68-21.41)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	31 (7) 27 [26-34] (19-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)		16.89 (0.55) 16.91 [16.51-17.24] (15.16-18.71)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		27.5 (5.9) 24.4 [23.7-30.1] (16.5-44.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

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3.1.3.2 Slower rate

3.1.3.2.1 Non-binding futility

3.1.3.2.1.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 41: SLOWER RATE: POWER AND TYPE I ERROR (ASSUMING NON-BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	900/ 992 (91%)	92/ 992 (9.3%)	916/ 980 (93%)	64/ 980 (6.5%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	238/ 985 (24%)	747/ 985 (76%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			142/ 969 (15%)	827/ 969 (85%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	885/ 992 (89%)	107/ 992 (11%)	896/ 980 (91%)	84/ 980 (8.6%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	250/ 985 (25%)	735/ 985 (75%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6			168/ 969 (17%)	801/ 969 (83%)

[1]n/ N (%)

3.1.3.2.1.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 42: SLOWER RATE: STOPPING REASON AND SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 980[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	846/ 992 (85%)	
						Reached sample size cap	5/ 992 (0.5%)	869/ 980 (89%)
						Superiority at interim analysis	141/ 992 (14%)	111/ 980 (11%)
						Sample size	303 (67) 315 [305-325] (110-450)	378 (67) 400 [400-400] (134-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	226/ 985 (23%)	
						Superiority at interim analysis	759/ 985 (77%)	
						Sample size	214 (98) 188 [130-306] (110-449)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		149/ 969 (15%)
						Superiority at interim analysis		820/ 969 (85%)
						Sample size		228 (97) 162 [153-315] (134-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	840/ 992 (85%)	

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 992[1]	SRS 2 N = 980[1]
						Reached sample size cap	2/ 992 (0.2%)	853/ 980 (87%)
						Superiority at interim analysis	150/ 992 (15%)	127/ 980 (13%)
						Sample size	303 (66) 314 [305-324](114-450)	375 (70) 400 [400-400](137-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Max recruitment period	235/ 985 (24%)	
						Superiority at interim analysis	750/ 985 (76%)	
						Sample size	218 (99) 192 [131-313](114-445)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Stopping reason		
						Reached sample size cap		168/ 969 (17%)
						Superiority at interim analysis		801/ 969 (83%)
						Sample size		236 (99) 164 [154-324](136-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 43: SLOWER RATE: SAMPLE SIZE (ASSUMING NON-BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 998[1]	Treatment 1 N = 998[1]	Treatment 2 N = 998[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	721 (247) 662 [429-979] [362-1,090]	214 (98) 188 [130-306] [110-449]	218 (99) 192 [131-313] [114-445]
	450	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	978 (97) 994 [973-1,015] [389-1,099]	303 (67) 315 [305-325] [110-450]	303 (66) 314 [305-324] [114-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	767 (257) 798 [497-978] [434-1,273]	228 (97) 162 [153-315] [134-400]	236 (99) 164 [154-324] [136-400]
	400	1,1	1.1 - 0.83	No futility rules	TRUE	0.4 vs 0.6	1,206 (143) 1,265 [1,258-1,269] [437-1,283]	378 (67) 400 [400-400] [134-400]	375 (70) 400 [400-400] [137-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.3.2.1.3 Timing of the trial analyses

TABLE 44: SLOWER RATE: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING NON-BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 992[1]	SRS 2 N = 980[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	19.72 (0.52) 19.73 [19.36-20.09] (17.63-21.64)	17.30 (0.44) 17.31 [16.98-17.60] (15.86-18.98)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	41.9 (5.3) 44.0 [44.0-44.0] (25.4-44.0)	38.4 (4.6) 40.0 [39.0-41.0] (23.2-44.0)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)	19.72 (0.52) 19.73 [19.35-20.09] (17.63-21.64)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	32.9 (7.1) 31.8 [26.7-39.0] (24.6-44.0)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time first interim analysis (months)		17.30 (0.44) 17.31 [16.98-17.60] (15.86-18.98)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	No futility rules	TRUE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		28.0 (5.1) 24.8 [24.2-30.6] (23.0-42.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)

3.1.3.2.2 Binding futility

3.1.3.2.2.1 Type I and power

The following table presents results of the type I error (probability to reach superiority while TRUE POR = 1) and power (probability to reach superiority while TRUE POR > 1) at the final analysis.

TABLE 45: SLOWER RATE: POWER AND TYPE I ERROR (ASSUMING BINDING FUTILITY)

Group	TRUE POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Subgroup 1		Subgroup 2	
						No Superiority [1]	Superiority [1]	No Superiority [1]	Superiority [1]
Treatment1									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	897/ 989 (91%)	92/ 989 (9.3%)	920/ 978 (94%)	58/ 978 (5.9%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	262/ 987 (27%)	725/ 987 (73%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			180/ 966 (19%)	786/ 966 (81%)
Treatment2									
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	900/ 989 (91%)	89/ 989 (9.0%)	906/ 978 (93%)	72/ 978 (7.4%)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	290/ 987 (29%)	697/ 987 (71%)		
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6			206/ 966 (21%)	760/ 966 (79%)

[1]n/ N (%)

3.1.3.2.2.2 Stopping reason and Sample size

The following table presents reason why the trial stopped and the sample size for each scenario.

TABLE 46: SLOWER RATE: STOPPING REASON AND SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 978[1]
Treatment1								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	574/ 989 (58%)	576/ 978 (59%)
						Max recruitment period	232/ 989 (23%)	
						Reached sample size cap	39/ 989 (3.9%)	296/ 978 (30%)
						Superiority at interim analysis	144/ 989 (15%)	106/ 978 (11%)
						Sample size	209 (130) 170 [71-320] (60-450)	234 (137) 208 [74-400] (62-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	92/ 987 (9.3%)	
						Max recruitment period	144/ 987 (15%)	
						Reached sample size cap	8/ 987 (0.8%)	
						Superiority at interim analysis	743/ 987 (75%)	
						Sample size	199 (101) 139 [129-260] (61-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		74/ 966 (7.7%)
						Reached sample size cap		110/ 966 (11%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 978[1]
						Superiority at interim analysis		782/ 966 (81%)
						Sample size		211 (96) 160 [151-286] (65-400)
Treatment2								
	POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	595/ 989 (60%)	579/ 978 (59%)
						Max recruitment period	211/ 989 (21%)	
						Reached sample size cap	45/ 989 (4.6%)	291/ 978 (30%)
						Superiority at interim analysis	138/ 989 (14%)	108/ 978 (11%)
						Sample size	201 (130) 159 [70-313](59-450)	233 (136) 199 [75-400](61-400)
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis	118/ 987 (12%)	
						Max recruitment period	137/ 987 (14%)	
						Reached sample size cap	7/ 987 (0.7%)	
						Superiority at interim analysis	725/ 987 (73%)	
						Sample size	194 (100) 137 [128-255](60-450)	
	POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Stopping reason		
						Futility at interim analysis		78/ 966 (8.1%)
						Reached sample size cap		127/ 966 (13%)
						Superiority at interim analysis		761/ 966 (79%)

Group	POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS1 vs SRS2	Characteristic	SRS 1 N = 989[1]	SRS 2 N = 978[1]
						Sample size		217 (100) 161 [152-308](62-400)

[1]n/ N (%); Mean (SD) Median [Q1-Q3] (Min-Max)

TABLE 47: SLOWER RATE: SAMPLE SIZE (ASSUMING BINDING FUTILITY)

Group	Sample size cap	TRUE POR (POR 1,POR 2)	Efficacy stopping rule (POR eff - peff)	Futility stopping rule (POR fut - pfut)	Triggers not implemented at first interim analysis	SRS1 vs SRS2	total N = 997[1]	Treatment 1 N = 997[1]	Treatment 2 N = 997[1]
SRS 1									
	450	1.37,1.37	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	663 (243) 629 [419-896] [193-1,090]	199 (101) 139 [129-260] [61-450]	194 (100) 137 [128-255] [60-450]
	450	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	708 (299) 829 [417-980] [190-1,099]	209 (130) 170 [71-320] [60-450]	201 (130) 159 [70-313] [59-450]
SRS 2									
	400	1.42,1.42	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	714 (243) 778 [490-878] [210-1,270]	211 (96) 160 [151-286] [65-400]	217 (100) 161 [152-308] [62-400]
	400	1,1	1.1 - 0.83	1.1 - 0.8	FALSE	0.4 vs 0.6	797 (329) 879 [491-996] [199-1,281]	234 (137) 208 [74-400] [62-400]	233 (136) 199 [75-400] [61-400]

[1]Mean (SD) Median [Q1-Q3] [Min-Max]

3.1.3.2.2.3 Timing of the trial analyses

TABLE 48: SLOWER RATE: TIME OF FIRST INTERIM ANALYSIS (MONTHS) AND TIME OF THE FINAL ANALYSIS (MONTHS) (ASSUMING BINDING FUTILITY)

POR	Efficacy stopping rule	Futility stopping rule	Triggers not implemented at first interim analysis	SRS 1 SRS1 vs SRS2	Analysis	SRS 1 N = 989[1]	SRS 2 N = 978[1]
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	19.72 (0.52) 19.73 [19.36-20.09] (17.63-21.64)	17.30 (0.44) 17.31 [16.99-17.60] (15.86-18.98)
POR=1,1 (type I error)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	31 (9) 27 [21-44] (19-44)	28 (8) 25 [19-35] (17-42)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)	19.72 (0.52) 19.73 [19.35-20.09] (17.63-21.64)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.37(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)	31 (7) 27 [27-34] (19-44)	
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time first interim analysis (months)		17.30 (0.44) 17.31 [16.99-17.60] (15.86-18.98)
POR 1=1.37 (SRS1) POR 1=1.42 (SRS2) POR 2=1.42(power)	POR_eff=1.1 - peff=0.83	PORfut=1.1 - Pfut= 0.8	FALSE	0.4 vs 0.6	Time final analysis for treatment 1 (months)		26.8 (4.9) 24.6 [24.1-30.3] (17.2-41.0)

[1]Mean (SD) Median [Q1-Q3] (Min-Max)