concordance=TRUE

Operating Characteristics of a Phase 3 Multi-Center, Group-Sequentially Monitored, Randomized, Controlled, Double-Blind, Efficacy Study of an Arbitrary Candidate SARS-CoV-2 Vaccine

`seqDesign` Output

August 28, 2020

Simulation Set-up

- $N = 27000$ SARS-CoV-2-negative participants at baseline, randomly allocated in the 2:1 ratio to vaccine vs. placebo (assuming 10% of the randomized 30000 participants are SARS-CoV-2-positive at baseline)
- All operating characteristics are for the 27000 baseline negative participants (18000 in the vaccine arm, 9000 in the placebo arm)
- 175 primary endpoints occurring ≥ 15 days after the first dose in the FAS cohort (henceforth referred to as the FAS-15d+ endpoints) is the target endpoint total for the event-driven primary analysis
- Efficacy monitoring at 35%, 70%, and 100% of the target 175 FAS-15d+ endpoints in the FAS cohort
- Non-efficacy monitoring at 20%, 60%, and 100% of approximately 108 endpoints occurring ≥ 15 days after the second dose (henceforthh referred to as the PP-15d+ endpoints) in the PP cohort
  - The PP cohort includes all FAS participants who received the second dose
- 3-month uniform accrual
- 25 months of participant follow-up (i.e., 2 years of follow-up post-vaccination)
- 1.556% 6-month COV-DIS incidence rate in the placebo arm
  - Chosen as the minimal incidence rate satisfying the requirement that the target numbers of FAS-15d+ endpoints under both 2:1 and 1:1 allocation ratios be accrued with 80% probability by 6.5 months since trial initiation in the scenario with $\overline{VE}$(2–32 weeks) = 60% (see below for description of the VE model)
- Stepwise VE model (all tables and figures are labeled by the time-averaged VE level over the time interval of (2, 32] weeks of follow-up denoted by $\overline{VE}$(2–32)):

Time Period (Weeks)	VE Level
(0, 2]	$0.1 \times (45/43) \times \overline{VE}(2\text{–}32)$
(2, 6]	$(2/3) \times (45/43) \times \overline{VE}(2\text{–}32)$
(6, 32]	$(45/43) \times \overline{VE}(2\text{–}32)$
(32, 108]	$\overline{VE}(2\text{–}32)$

- 2% annual dropout in each arm
- 2% probability of a missed second dose (used in definition of the PP cohort)
- Group-sequential monitoring for benefit/efficacy: a group-sequential one-sided Wald test of H_0: VE $\leq 30\%$ using the Cox model and the O'Brien-Fleming boundary
  - Analyses performed when 62 (35% information fraction), 123 (70% information fraction), and 175 FAS-15d+ endpoints have been accrued (175 is the target number for powering the trial for $\overline{VE}(2\text{–}32) = 60\%$)
  - At the time of each analysis, testing of H_0 is performed in the FAS cohort including only FAS-15d+ endpoints
  - Reject H_0 if the lower bound of the monitoring-adjusted 95% Wald CI for VE is $> 30\%$
  - 0.025 overall type 1 error rate for 3 one-sided tests (2 interim and a primary analysis)
- Interim monitoring for lack of benefit/non-efficacy: a one-sided Wald test of H_0: VE $\geq 50\%$ using the Cox model and nominal 95% confidence intervals following Freidlin, Korn, and Gray (2010, *Clin Trials*) (referred to as the FKG approach)
  - Analyses performed when approximately 22 (20% information fraction), 65 (60% information fraction), and 108 PP-15d+ endpoints have been accrued
  - Timing of analyses harmonized with sequential monitoring for benefit/efficacy
  - At the time of each analysis, testing of H_0 is performed in the PP cohort including only PP-15d+ endpoints
  - Reject H_0 if the upper bound of the nominal 95% Wald CI for VE is $< 50\%$
  - Nominal 0.025 type 1 error rate of each of the 3 one-sided tests

- Summary of efficacy monitoring boundaries (using the Wald test)

Information Fraction (FAS-15d+ Endpoints)	Efficacy Monitoring (O'B-F) (Rejecting H_0: VE $\leq 30\%$)		
	Nominal Signif Level	Est. VE (Est. HR) at Bndary	Cum Prob of Crossing Bndary if $\overline{VE}(2\text{–}32) = 60\%$
35% (62)	0.000151	VE $\geq 73.3\%$ HR ≤ 0.2672	2.0%
70% (123)	0.007332	VE $\geq 54.9\%$ HR ≤ 0.4505	56.0%
100% (175)	0.022742	VE $\geq 48.3\%$ HR ≤ 0.5173	86.0%

- Summary of non-efficacy monitoring boundaries (using the Wald test)

Information Fraction (PP-15d+ Endpoints)	Non-Efficacy Monitoring (FKG) (Rejecting H_0: VE $\geq 50\%$)		
	Nominal Signif Level	Est. VE (Est. HR) at Bndary	Cum Prob of Crossing Bndary if $\overline{VE}(2\text{–}32) = 0\%$
20% (22)	0.025	VE $\leq -26.4\%$ HR ≥ 1.2637	38.0%
60% (65)	0.025	VE $\leq 17.4\%$ HR ≥ 0.8257	76.0%
100% (108)	0.025	VE $\leq 26.6\%$ HR ≥ 0.7342	94.0%

- Cumulative probabilities of crossing the non-efficacy boundary at 22, 65, and 108 PP-15d+ endpoints if $\overline{VE}(2\text{–}32) = 60\%$ are $< 0.1\%$, $< 0.1\%$, and $< 0.1\%$
- Interim monitoring for potential vaccine harm/disease enhancement: monitoring-adjusted one-sided conditional exact binomial test of H_0: $p_v \geq N_v/N$, where p_v is the binomial probability of assignment to the vaccine arm conditional on the observed number of endpoints, and N_v/N is the proportion of participants randomized to the vaccine arm
  - Starting at the 12^{th} FAS-15d+ endpoint and then continuously (i.e., after each FAS-15d+ endpoint) until the first interim analysis for lack of benefit (at 62 FAS-15d+ endpoints)
  - 0.05 overall type 1 error rate and a constant nominal significance level of each test
- 1000 Monte-Carlo iterations

Table 1: Probabilities (×100) of reaching each possible trial monitoring outcome and unconditional power (×100) to reject H_0: $VE \leq 30\%$ in the FAS and PP cohorts counting only FAS-15d+ and PP-15d+ endpoints, respectively, for a 2-arm study design with 9000 placebo and 18000 vaccine recipients

		Harm	Non-eff	Uncond Power	
$\overline{VE}$(2–32)	$\overline{HR}$(2–32)	FAS[‡] VE< 0%	PP[†] VE<50%	FAS[‡] VE>30%	PP[†] VE>30%
-200%	3.0	78.0	22.0	0.0	0.0
-150%	2.5	66.0	34.0	0.0	0.0
-100%	2.0	52.0	48.0	0.0	0.0
-50%	1.5	26.0	74.0	0.0	0.0
0%	1.0	4.0	94.0	0.0	0.0
10%	0.9	2.0	84.0	0.0	0.0
20%	0.8	4.0	66.0	0.0	0.0
30%	0.7	2.0	36.0	6.0	6.0
40%	0.6	0.0	12.0	10.0	26.0
50%	0.5	0.0	0.0	50.0	56.0
60%	0.4	2.0	0.0	86.0	92.0
70%	0.3	0.0	0.0	100.0	100.0
80%	0.2	2.0	0.0	98.0	98.0
90%	0.1	2.0	0.0	98.0	98.0

[†] PP cohort counting only PP-15d+ endpoints

[‡] FAS cohort counting only FAS-15d+ endpoints

N=9000:18000 placebo:vaccine group

3.11% annual incidence rate in placebo group

2% annual dropout rate in each group

Cox model-based efficacy monitoring with O'Brien-Fleming boundaries (FAS-15d+ endpoints)

Cox model-based non-efficacy monitoring with nominal CIs (PP-15d+ endpoints)

Cox model-based unconditional power

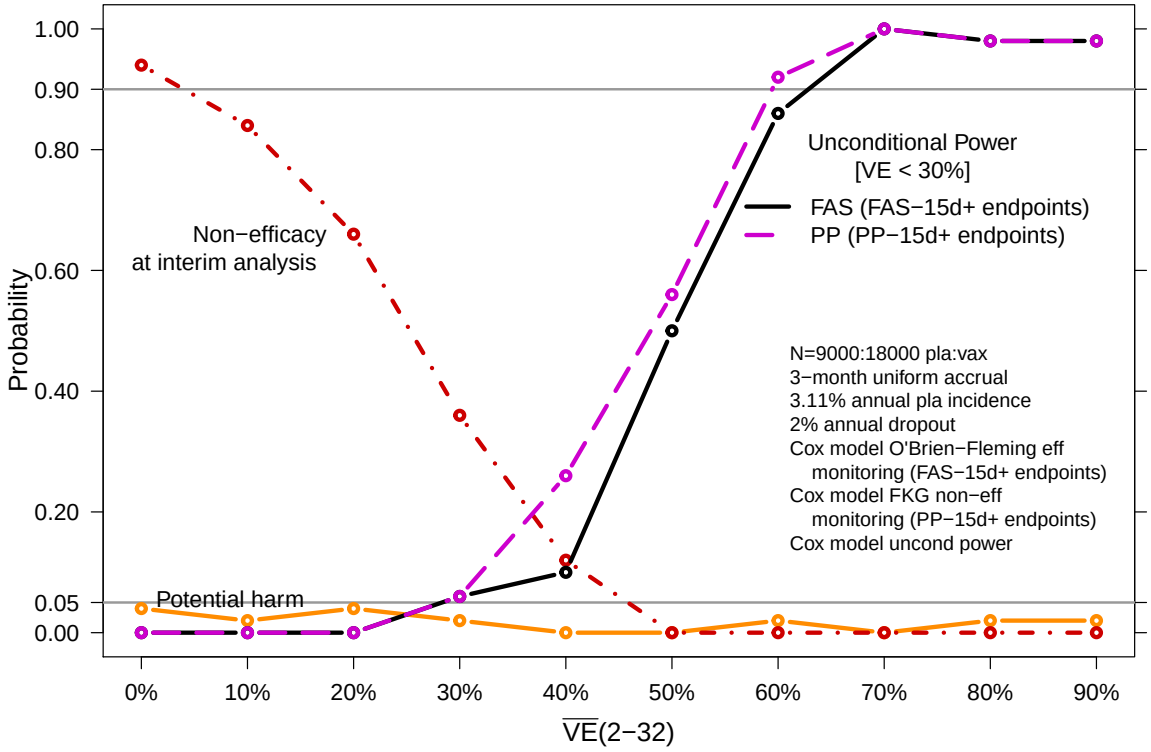

Figure 1: Probabilities of reaching each possible trial monitoring outcome, and unconditional powers to reject H_0: $VE \leq 30\%$ in the FAS and PP cohorts counting only FAS-15d+ and PP-15d+ endpoints, respectively, for a 2-arm study design with 9000 placebo and 18000 vaccine recipients

Table 2: Probabilities ($\times 100$) of rejecting H_0: VE $\leq$ 30% at the first interim analysis, second interim analysis, and the primary analysis

	Rejecting VE $\leq$ 30%		
$\overline{VE}$(2–32)	1st IA	2nd IA	Prim A
-200%	0.0	0.0	0.0
-150%	0.0	0.0	0.0
-100%	0.0	0.0	0.0
-50%	0.0	0.0	0.0
0%	0.0	0.0	0.0
10%	0.0	0.0	0.0
20%	0.0	0.0	0.0
30%	0.0	0.0	6.0
40%	0.0	4.0	6.0
50%	0.0	10.0	40.0
60%	2.0	54.0	30.0
70%	4.0	90.0	6.0
80%	22.0	76.0	0.0
90%	78.0	20.0	0.0

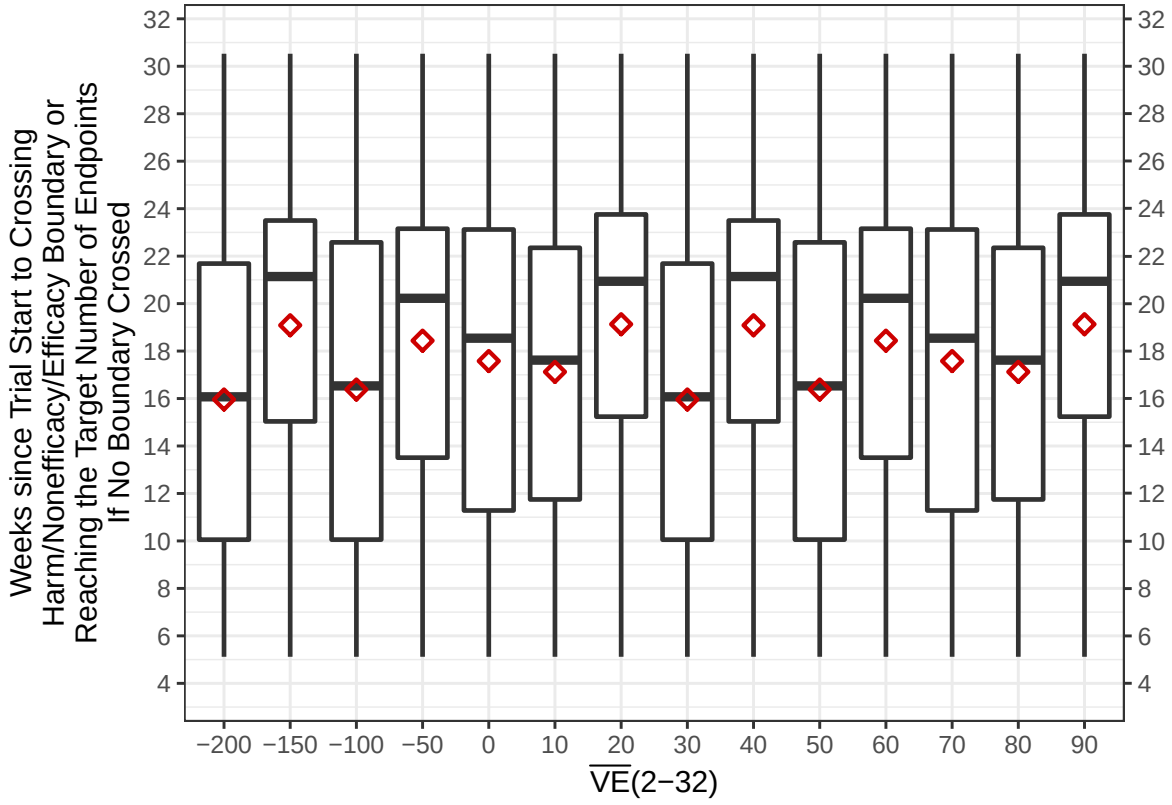

Figure 2: Probability distribution of time (in weeks) since trial start to crossing the harm, nonefficacy or efficacy boundary or reaching the target number of endpoints if no boundary is crossed. The diamonds show the mean.

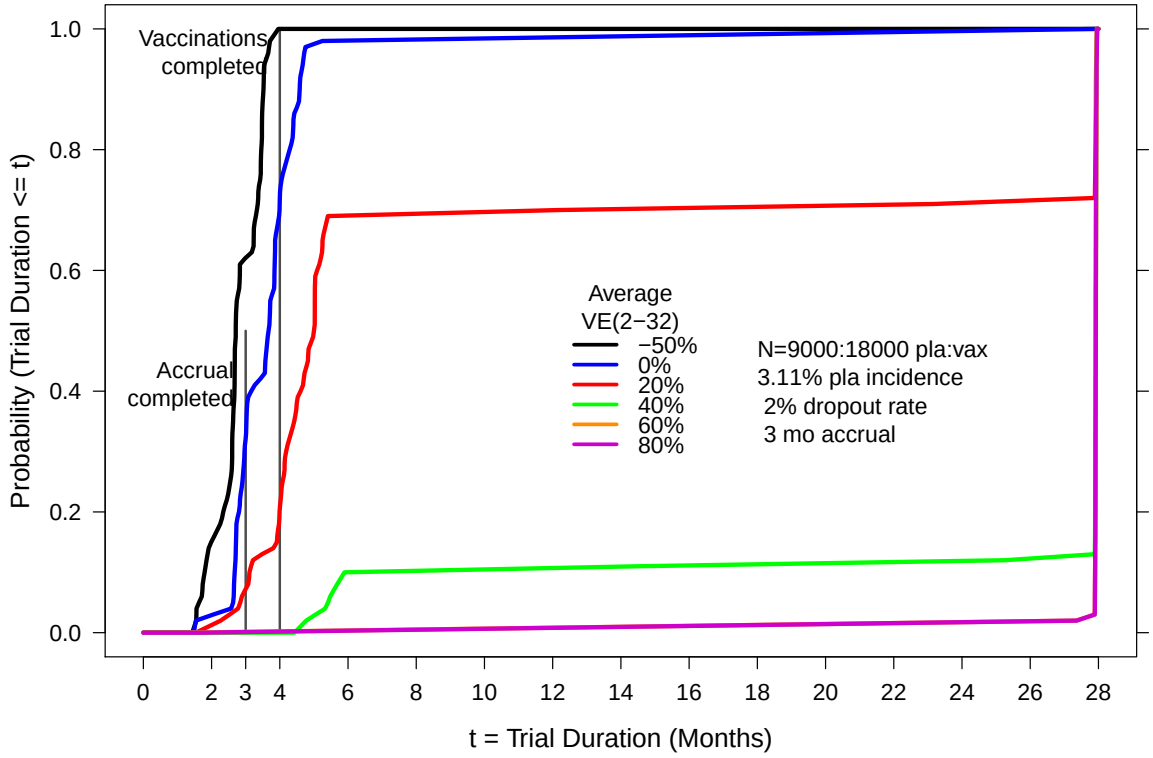

Figure 3: Distribution of trial duration with 25 months of follow-up (n =9000 in the placebo arm and n =18000 in the vaccine arm)

Table 3: Median time since the first vaccination to accrue given COV-DIS endpoint totals occurring more that 14 days after the first vaccination in the FAS cohort and those occurring more than 14 days after the last vaccination in the PP cohort, under $\overline{VE}(2\text{–}32) = 60\%$ with the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, 25 months of participant follow-up, 3.11% annual placebo incidence rate, 2% annual dropout rate, and 2% probability of a missed second dose).

Endpoint Total	Med Months* FAS†	Med Months* PP‡
30	2.5	3.6
40	2.8	3.9
50	3.0	4.3
60	3.3	4.5
62	3.4	4.6
70	3.6	4.8
80	3.8	5.1
90	4.1	5.3
100	4.3	5.6
110	4.6	5.8
120	4.9	6.1
123	4.9	6.2
130	5.1	6.3
140	5.3	6.6
150	5.6	6.9
160	5.9	7.1
170	6.1	7.4
175	6.3	7.5
180	6.4	7.6
190	6.6	7.9
200	6.9	8.1

* Median time (in months) since first enrollment

† Endpoints in the FAS cohort starting > 14 days after enrollment

‡ Endpoints in the PP cohort starting > 14 days after completed immunization

Table 4: 80^{th} percentile of the distribution of time since the trial start to accrue given COV-DIS endpoint totals occurring more that 14 days after the first vaccination in the FAS cohort and those occurring more than 14 days after the last vaccination in the PP cohort, under $\overline{VE}(2\text{–}32) = 60\%$ with the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, 25 months of participant follow-up, 3.11% annual placebo incidence rate, 2% annual dropout rate, and 2% probability of a missed second dose).

Endpoint Total	80^{th} %ile Months* FAS†	80^{th} %ile Months* PP‡
30	2.6	3.8
40	2.9	4.2
50	3.2	4.4
60	3.5	4.7
62	3.5	4.8
70	3.7	5.0
80	4.0	5.2
90	4.2	5.5
100	4.5	5.7
110	4.8	6.0
120	5.0	6.3
123	5.1	6.4
130	5.3	6.5
140	5.6	6.8
150	5.8	7.0
160	6.1	7.3
170	6.3	7.5
175	6.4	7.7
180	6.6	7.8
190	6.9	8.1
200	7.1	8.4

* 80^{th} percentile of time (in months) since first enrollment

† Endpoints in the FAS cohort starting > 14 days after enrollment

‡ Endpoints in the PP cohort starting > 14 days after completed immunization

Table 5: Median time since the first vaccination to accrue given COV-DIS endpoint totals occurring more that 14 days after the first vaccination in the FAS cohort and those occurring more than 14 days after the last vaccination in the PP cohort, under $\overline{VE}(2\text{–}32) = 80\%$ with the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, 25 months of participant follow-up, 3.11% annual placebo incidence rate, 2% annual dropout rate, and 2% probability of a missed second dose).

Endpoint Total	Med Months* FAS†	Med Months* PP‡
30	2.7	3.9
40	3.0	4.3
50	3.3	4.6
60	3.6	5.0
62	3.7	5.1
70	3.9	5.3
80	4.3	5.7
90	4.6	6.0
100	4.9	6.3
110	5.3	6.7
120	5.7	7.0
123	5.7	7.1
130	5.9	7.4
140	6.3	7.7
150	6.6	8.1
160	6.9	8.4
170	7.2	8.7
175	7.4	8.9
180	7.6	9.1
190	8.0	9.5
200	8.3	9.8

* Median time (in months) since first enrollment

† Endpoints in the FAS cohort starting > 14 days after enrollment

‡ Endpoints in the PP cohort starting > 14 days after completed immunization

Table 6: 20^{th} percentile of the distribution of COV-DIS endpoint totals occurring more that 14 days after the first vaccination in the FAS cohort and those occurring more than 14 days after the last vaccination in the PP cohort observed by a given time since the first vaccination, under $\overline{VE}(2\text{–}32) = 60\%$ with the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, 25 months of participant follow-up, 3.11% annual placebo incidence rate, 2% annual dropout rate, and 2% probability of a missed second dose).

Months*	20^{th} %ile Endpoints FAS†	20^{th} %ile Endpoints PP‡
1	0	0
2	14	0
3	42	11
4	81	35
5	117	71
6	157	110
7	196	147
8	237	188
9	272	221
10	314	261
11	355	303
12	392	339

* Months since first enrollment

† 20^{th} percentile endpoints in the FAS cohort starting > 14 days after enrollment

‡ 20^{th} percentile endpoints in the PP cohort starting > 14 days after completed immunization

Table 7: Distribution of the number of month 0.5–7 FAS and month 1.5–7 PP COV-DIS endpoints in the vaccine group, for scenarios with $\overline{VE}(2\text{–}32) = 90\%$ and the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, and per-protocol cohort is identified assuming 2% probability of ≥ 1 missed vaccination).

	Percentiles of distribution of # of COV-DIS endpoints in vax arm						
Mean	1%	5%	25%	50%	75%	95%	99%
Month 0.5–7 COV-DIS endpoints in the FAS cohort							
32	12	22	27	33	35	42	46
Month 1.5–7 COV-DIS endpoints in PP* cohort							
14	3	9	11	15	18	19	23

N=9000:18000 Placebo:vaccine arm

3.11% annual incidence rate in placebo arm

$\overline{VE}(2\text{–}32) = 90\%$

2% dropout rate in each arm

*2% probability of a missed second dose

Table 8: Distribution of the number of month 0.5–13 FAS and month 1.5–13 PP COV-DIS endpoints in the vaccine group, for scenarios with $\overline{VE}(2\text{–}32) = 90\%$ and the VE model described in the simulation setup ($N = 9000$ in the placebo group, $N = 18000$ in the vaccine group, and per-protocol cohort is identified assuming 2% probability of ≥ 1 missed vaccination).

	Percentiles of distribution of # of COV-DIS endpoints in vax arm						
Mean	1%	5%	25%	50%	75%	95%	99%
Month 0.5–13 COV-DIS endpoints in the FAS cohort							
58	24	49	54	58	62	68	74
Month 1.5–13 COV-DIS endpoints in PP* cohort							
40	13	30	38	40	44	48	53

N=9000:18000 Placebo:vaccine arm

3.11% annual incidence rate in placebo arm

$\overline{VE}(2\text{–}32) = 90\%$

2% dropout rate in each arm

*2% probability of a missed second dose

Table 9: Month 0.5-7 COV-DIS primary endpoint splits in the FAS cohort and 95% confidence bounds for VE at the time of stopping the trial

Ave VE(0–6) (%)	Vaccine: Placebo*	VE 95% LB† (%)	VE 95% UB† (%)
0	81:38	−45	31
40	174:147	24	52
50	149:147	36	61
60	120:146	48	69
70	88:148	61	77
80	60:148	73	85

* Median endpoint counts

† Under proportional hazards

Table 10: COV-DIS endpoint splits occurring ≥ 15 days after the last vaccination in the PP cohort, and point estimates of VE at the non-efficacy boundary using Freidlin et al.'s nominal CI approach

Total Endpoints†	Vaccine: Placebo*	Est. VE (%)
66	41:25	17
99	60:39	24
131	77:54	28

* Under VE := 1 − vax-arm attack rate/ /pla-arm attack rate

† Scenario with VE = 0%