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

December 31, 2020

Contents

Simulation Set-up

- This report envisages a design with a *single* vaccine arm; all operating characteristics extend to each of multiple vaccine arms assuming independent evaluation of efficacy in each vaccine arm vs. the shared placebo arm
- $N = 27000$ SARS-CoV-2-negative participants at baseline, randomly allocated in the 1:1 ratio to vaccine vs. placebo (if 10% of the randomized participants are SARS-CoV-2-positive at baseline, then the total sample size is $27000/0.9 = 30000$)
- All operating characteristics are for the 27000 baseline negative participants (13500 in the vaccine arm, 13500 in the placebo arm)
- 3.1% annual 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)
- 197 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 197 FAS-15d+ endpoints in the FAS cohort
- Non-efficacy monitoring at 20%, 60%, and 100% of approximately 130 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)
- 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]	$0.1 \times (45/43) \times \overline{VE}$(2–32)
(2, 6]	$(2/3) \times (45/43) \times \overline{VE}$(2–32)
(6, 32]	$(45/43) \times \overline{VE}$(2–32)
(32, 108]	$\overline{VE}$(2–32)

- 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 69 (35% information fraction), 138 (70% information fraction), and 197 FAS-15d+ endpoints have been accrued (197 is the target number for powering the trial for $\overline{VE}$(2–32) = 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 26 (20% information fraction), 78 (60% information fraction), and 130 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) % latex table generated in R 4.0.3 by xtable 1.8-4 package % Wed Dec 30 14:40:41 2020

		Efficacy Monitoring (O'Brien-Fleming) (Rejecting H_0: VE $\leq 30\%$)			
FAS-15d+ Endpoints	Inf Frac	Nominal Signif Level	Est. VE at Bndary	Adj. 95% CI* at Bndary	Cum Prob of Crossing Bndary if $\overline{VE}(2\text{–}32) = 60\%$
69	35%	0.000151	VE $\geq 77.1\%$	$(30.0\%, 92.5\%)$	0.1%
138	70%	0.007332	VE $\geq 55.4\%$	$(30.0\%, 71.5\%)$	50.5%
197	100%	0.022742	VE $\geq 48.2\%$	$(30.0\%, 61.6\%)$	90.4%

* Group-sequential monitoring-adjusted 95% CI

- Summary of non-efficacy monitoring boundaries (using the Wald test) % latex table generated in R 4.0.3 by xtable 1.8-4 package % Wed Dec 30 14:40:42 2020

		Non-Efficacy Monitoring (FKG) (Rejecting H_0: VE $\geq 50\%$)			
PP-15d+ Endpoints	Inf Frac	Nominal Signif Level	Est. VE at Bndary	95% CI* at Bndary	Cum Prob of Crossing Bndary if $\overline{VE}(2\text{–}32) = 0\%$
26	20%	0.025	VE $\leq -7.9\%$	$(-132.9\%, 50.0\%)$	38.9%
78	60%	0.025	VE $\leq 21.8\%$	$(-22.3\%, 50.0\%)$	80.6%
130	100%	0.025	VE $\leq 29.1\%$	$(-0.5\%, 50.0\%)$	92.2%

* Nominal 95% CI

- Cumulative probabilities of crossing the non-efficacy boundary at 26, 78, and 130 PP-15d+ endpoints if $\overline{VE}(2\text{–}32) = 60\%$ are 0.2%, 0.2%, and 0.2%
- 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 69 FAS-15d+ endpoints)
  - 0.05 overall type 1 error rate and a constant nominal significance level of each test
- 1000 Monte-Carlo iterations
- Software: R package `seqDesign` available at https://github.com/mjuraska/seqDesign

Power Calculations

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 13500 placebo and 13500 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	88.3	11.7	0.0	0.0
-150%	2.5	73.6	26.4	0.0	0.0
-100%	2.0	50.6	49.4	0.0	0.0
-50%	1.5	23.5	76.5	0.0	0.0
0%	1.0	5.5	92.2	0.0	0.0
10%	0.9	2.9	91.3	0.1	0.0
20%	0.8	1.8	74.9	0.2	0.4
30%	0.7	1.1	50.2	1.4	3.7
40%	0.6	1.1	19.0	13.1	17.6
50%	0.5	1.2	3.2	50.9	56.5
60%	0.4	0.2	0.2	90.4	93.9
70%	0.3	0.1	0.0	99.9	99.9
80%	0.2	0.2	0.0	99.8	99.8
90%	0.1	0.0	0.0	100.0	100.0

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

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

N=13500:13500 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

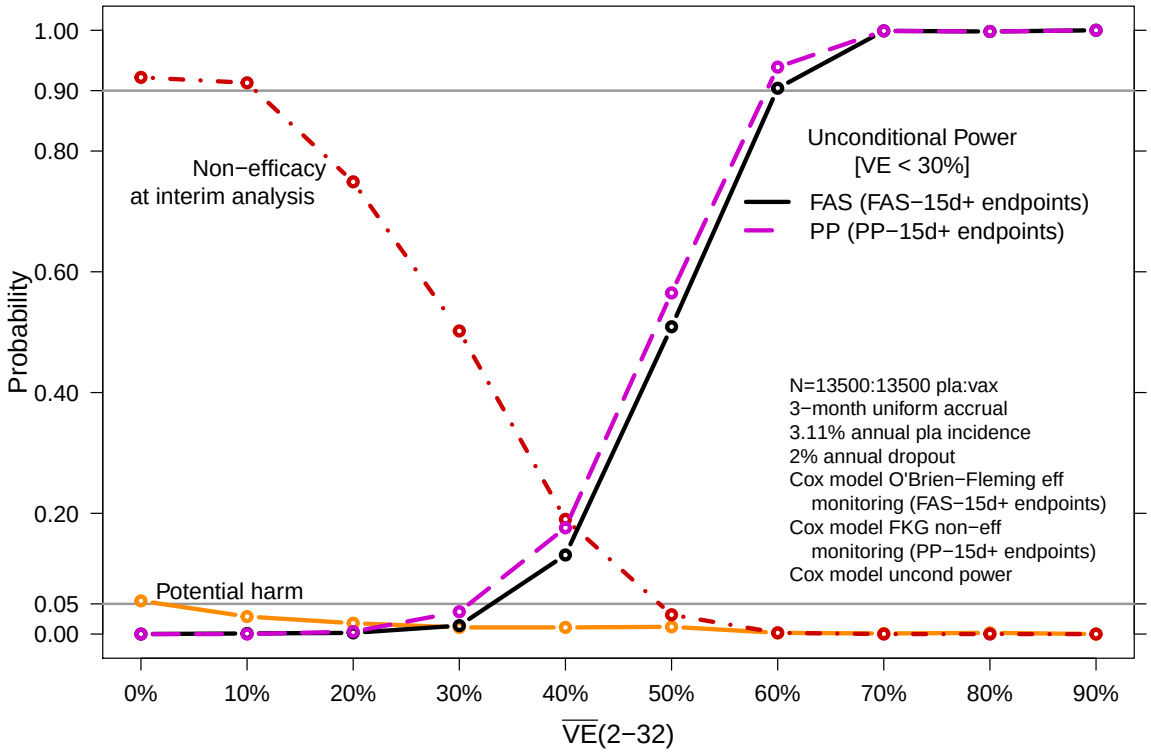

Figure 1: Probabilities of reaching each possible trial monitoring outcome, and unconditional powers to reject H_0: $VE \leq 30\%$ in the FAS and PP cohorts counting only FAS-15d+ and PP-15d+ endpoints, respectively, for a 2-arm study design with 13500 placebo and 13500 vaccine recipients

Interim Monitoring

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	0.1
20%	0.0	0.0	0.2
30%	0.0	0.5	0.9
40%	0.0	2.6	10.5
50%	0.0	12.7	38.2
60%	0.1	50.4	39.9
70%	1.2	88.0	10.7
80%	10.7	88.9	0.2
90%	48.7	51.3	0.0

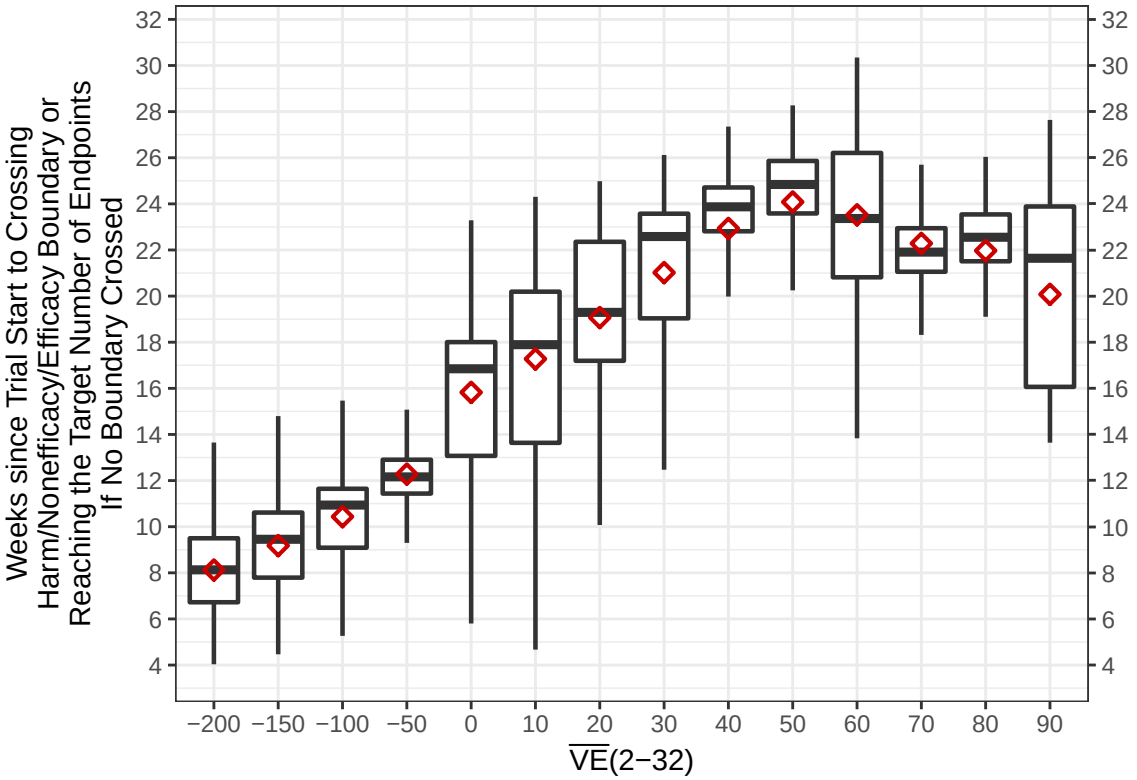

Figure 2: Probability distribution of time (in weeks) since trial start to crossing the harm, nonefficacy or efficacy boundary or reaching the target number of endpoints if no boundary is crossed. The diamonds show the mean.

Trial Duration

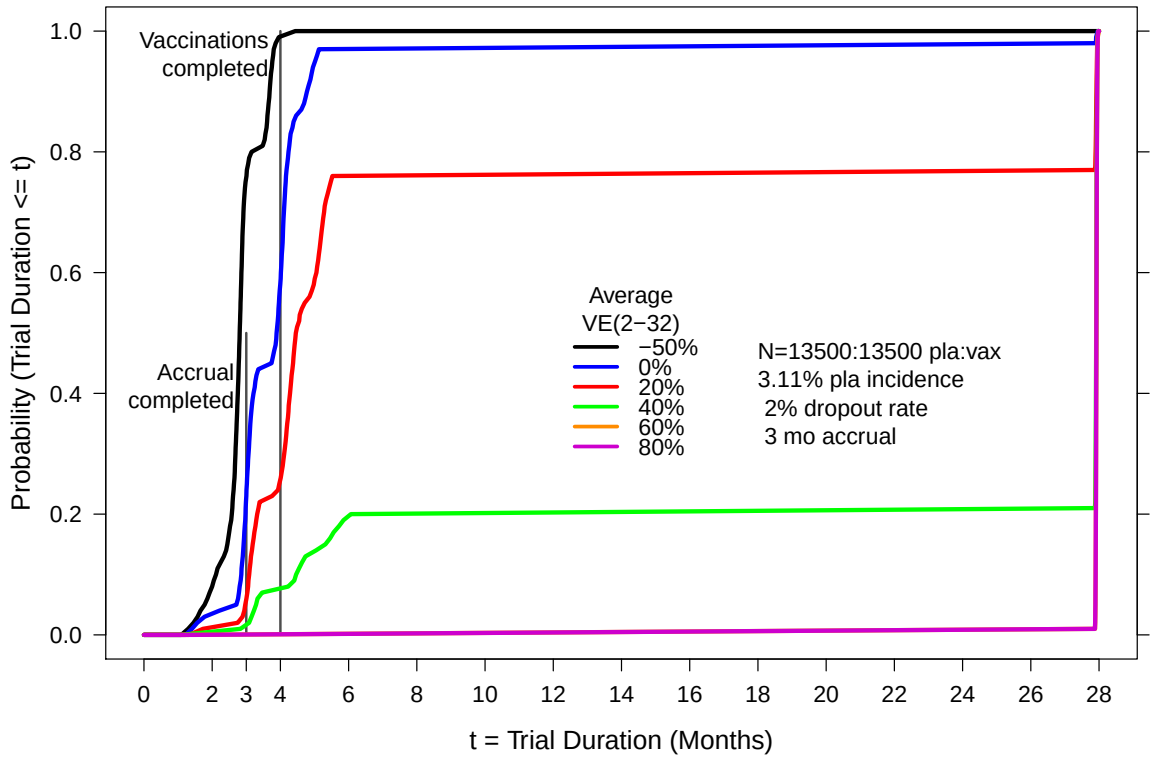

Figure 3: Distribution of trial duration with 25 months of follow-up (n =‘r format(N.pla, scientific=FALSE)‘ in the placebo arm and n =‘r format(N.vax, scientific=FALSE)‘ in the vaccine arm)

Endpoint Accrual

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 ($N = 13500$ in the placebo group, $N = 13500$ 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	2.4	3.4
40	2.7	3.7
50	3.0	4.0
60	3.2	4.3
69	3.4	4.5
70	3.4	4.5
80	3.6	4.7
90	3.8	4.9
100	4.0	5.1
110	4.2	5.4
120	4.4	5.6
130	4.6	5.8
138	4.8	6.0
140	4.8	6.0
150	5.1	6.2
160	5.3	6.4
170	5.5	6.6
180	5.7	6.9
190	5.9	7.1
197	6.1	7.2
200	6.1	7.3

* 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 ($N = 13500$ in the placebo group, $N = 13500$ 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	3.6
40	2.9	3.9
50	3.1	4.2
60	3.3	4.4
69	3.6	4.6
70	3.6	4.6
80	3.8	4.9
90	4.0	5.1
100	4.2	5.3
110	4.4	5.5
120	4.6	5.8
130	4.8	6.0
138	5.0	6.2
140	5.1	6.2
150	5.3	6.5
160	5.5	6.7
170	5.7	6.9
180	6.0	7.1
190	6.2	7.3
197	6.3	7.5
200	6.4	7.6

* 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 ($N = 13500$ in the placebo group, $N = 13500$ 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	3.1	4.2
60	3.3	4.5
69	3.6	4.7
70	3.6	4.8
80	3.8	5.0
90	4.1	5.3
100	4.3	5.5
110	4.5	5.8
120	4.8	6.0
130	5.1	6.3
138	5.3	6.5
140	5.3	6.5
150	5.6	6.8
160	5.8	7.0
170	6.0	7.3
180	6.3	7.5
190	6.6	7.8
197	6.7	8.0
200	6.8	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 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 ($N = 13500$ in the placebo group, $N = 13500$ 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	1	0
2	15	1
3	45	14
4	90	43
5	136	85
6	182	129
7	228	174
8	274	219
9	319	263
10	365	309
11	412	355
12	456	400

* 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

Endpoints in Vaccine Arm for Correlates Evaluation

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 ($N = 13500$ in the placebo group, $N = 13500$ 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							
24	14	16	20	24	27	32	36
Month 1.5–7 COV-DIS endpoints in PP* cohort							
11	4	6	9	11	13	17	19

N=13500:13500 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 ($N = 13500$ in the placebo group, $N = 13500$ 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							
44	30	34	39	43	48	54	60
Month 1.5–13 COV-DIS endpoints in PP* cohort							
31	19	22	27	31	34	40	44

N=13500:13500 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