

STATISTICAL REVIEW AND EVALUATION

Memorandum

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Review Committee

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Subject Adenovirus Type-4 and Type-7 Vaccines, Live, Oral
BLA 125296/0

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EXECUTIVE SUMMARY

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study in military recruits to evaluate the safety and efficacy of oral Type-4 adenovirus (ADV) vaccine to prevent wild Type-4 ADV associated acute respiratory disease (ARD) and of oral Type-7 ADV vaccine to induce neutralizing antibody to Type-7 ADV. The study was conducted in a total of 4040 intent-to-treat (ITT) subjects, with a randomization ratio of 3:1 for the vaccine versus placebo groups, and had more than 80% power. The reduction in ARD attack rate (Day 56 post vaccination) due to wild Type-4 ADV was the primary endpoint for the pivotal efficacy evaluation. The seroconversion rate (SCR) at Day 26 post vaccination due to Type-7 ADV titer was also a primary efficacy variable.

Efficacy. Based on the wild ADV-4 febrile ARD attack rate of 0.07% observed in the vaccine arm compared to 4.76% in the placebo arm among the ITT subjects, the study showed a vaccine efficacy (VE) of 0.986 with its 2-sided 95% confidence interval (CI) as (0.952, 0.998). The 2-sided 95% CI lower bound of the VE exceeded the pre-specified threshold of 0.60, thereby establishing the vaccine's efficacy endpoint in terms of the reduction in wild ADV-4 febrile ARD attack rate. The efficacy endpoint was also met in terms of the vaccine's ADV Type-7

seroconversion rate. The SCR had a point estimate of 93.8% with 2-sided 95% CI: (92.3%, 95.2%). The SCR's lower bound of confidence exceeded the pre-specified threshold of 70%, establishing efficacy.

Lot Consistency. The study results supported the clinical lot consistency criteria for the three manufacturing lots. Based on the ADV-4 titer (at Day 26), the values for \log_e Titer mean \pm std were 4.46 ± 1.49 , 4.56 ± 1.41 , and 4.61 ± 1.37 in the three lots 1, 2, and 3, respectively. With the resulting GMT (95% CI) ratios of 0.92 (0.79, 1.08), 0.87 (0.75, 1.02) and 0.94 (0.81, 1.10), respectively for the comparisons between lots 1 and 2, 1 and 3, and 2 and 3, the two-sided 95% CIs on GMT ratios in lot pairs excluded both a $\frac{1}{2}$ -fold decrease and a 2-fold increase, the bounds that were pre-specified for lot consistency. Similar consistency results held based on the ADV-7 titer (at Day 26) as well, where the GMT ratios in the lot pairs were included within the pre-specified interval ($\frac{1}{2}$, 2).

Safety. In terms of safety, the study showed a comparable general safety profile with placebo. No death attributable to the study vaccine occurred during the trial. The incidence of any serious adverse events was 1.2% in both arms with no significant inter-arm difference (2-sided 95% CI on the rate difference: (-1.0%, +1.0%). Having observed the treatment emergent AE rates of 92.2% and 94.2% in the vaccine and placebo arms, respectively, the vaccine arm seemed to have lower rate than in the placebo arm, with the 2-sided 95% CI on the rate difference being (-3.6%, -0.1%). Also, an overall 71.2% of the subjects had AEs requiring medications, but the rate did not differ across arms (2-sided 95% CI on the rate difference: -6.0%, +0.4%).

Recommendation. In view of the efficacy and safety results as above, this review supports recommendation for the product's approval.

EFFICACY TRIAL Study DR-ADV-301

Title

“A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of DR-5001.”

Design

This was a phase-3, randomized, double-blind, placebo-controlled study, conducted in two centers (Fort Jackson, SC and Great Lakes, IL) to evaluate the safety and efficacy of oral Type-4 ADV vaccine to prevent wild Type-4 ADV associated ARD incidence and of oral Type-7 ADV vaccine to induce neutralizing antibody to Type-7 ADV. A total of 4000 healthy adult subjects with random allocation of 3:1 to the vaccine and placebo arms, respectively, were planned based upon 80% power. Eventually, the study randomized 4041 subjects. Of the 4041 subjects, 2010 were from Fort Jackson and the remaining 2031 subjects were from Great Lakes.

Primary Objectives

“To determine the efficacy of the oral Type-4 vaccine in reducing the attack rate of wild Type-4 ADV associated febrile ARD.”

“To determine the antibody response to the oral Type-7 ADV vaccine.”

Secondary Objectives

“To determine the antibody response to the oral Type-4 ADV vaccine.”

”To evaluate the safety and tolerability of the oral Type-4 and Type-7 ADV vaccine.”

Subjects Disposition

The study randomized a total of 4041 subjects for efficacy evaluation, one subject could not swallow the vaccine tablets, and 4040 subjects were administered the vaccines and as such served both as the intent-to-treat (ITT) and safety populations. Of the 4040 subjects, 3842 (95.1%) subjects completed the study, and the remaining 198 (4.9%) subjects did not. The reasons for discontinuation along with a detailed accounting of the 4040 subjects are given in Table 1. Of those who completed the study, 41 subjects vomited within the 24-hours of vaccine administration and 1 subject took corticosteroids within 7 days post vaccination, thereby causing these 42 subjects to be excluded from the per protocol population.

Two points should be noted: (1) all tables in this review were generated by the reviewer based on the applicant’s analytic files, and (2) all 95% confidence intervals are 2-sided.

Table 1: Subject Disposition.

	Vaccine (N=3032)	Placebo (N=1009)	Total (N=4041)
All Treated (ITT/Safety)	3031(99.97%)	1009(100.0%)	4040 (99.97%)
Completed Study	2887 (95.2%)	955 (94.6%)	3842 (95.1%)
Per Protocol	2855 (94.2%)	945 (93.7%)	3800 (94.0%)
Did Not Complete Study	144 (4.8%)	54 (5.4%)	198 (4.9%)
Discontinued due to:			
Did Not Meet Protocol Requirements	3 (0.1%)	3 (0.3%)	6 (0.1%)
Non Compliance with the Protocol	2 (0.1%)	2 (0.2%)	4 (0.1%)
Investigator Discretion	1 (0.0%)	0 (0.0%)	1 (0.0%)
Subject Request to be Withdrawn	17 (0.6%)	6 (0.6%)	23 (0.6%)
Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Pregnant	2 (0.1%)	0 (0.0%)	2 (0.0%)
Lost to Follow-Up	19 (0.6%)	8 (0.8%)	27 (0.7%)
Other	100 (3.3%)	35 (3.5%)	135 (3.3%)

Demographic Characteristics

The age, gender, and race distributions of the subjects are provided in Table 2. While these distributions are by and large similar across the two study arms, it can be stated that, overall, 62% of the subjects were white, 18% were African-American, and 20% comprised other races, all with a median age of 20 years.

Table 2: Demographic Characteristics, ITT Population.

Characteristics	ADV vaccine N= 3031	Placebo N = 1009	Total N = 4040
<u>Race</u>			
African-American	554 (18.3%)	186 (18.4%)	740 (18.3%)
Asian	94 (3.1%)	29 (2.9%)	123 (3.0%)
Caucasian	1871 (61.8%)	642 (63.6%)	2513 (62.2%)
Other	512 (16.8%)	152 (15.1%)	664 (16.4%)
<u>Gender</u>			
Male	1910 (63.0%)	642 (63.6%)	2552 (63.2%)
Female	1121 (37.0%)	367 (36.4%)	1488 (36.8%)
<u>Age (years)</u>			
Mean (Std)	21.3 (4.0)	21.1 (4.1)	21.2 (4.0)
Median	19.8	19.7	19.8
(Min, Max)	(17.1, 42.0)	(17.1, 42.2)	(17.1, 42.2)

Baseline Titer Characteristics

The baseline titer characteristics are presented in Table 3. A total of 2584 (64%) subjects were seronegative with ADV Type-4 titer and 1536 subjects were seronegative with ADV Type-7 titer. For each titer type, the proportion with seronegativity was by and large comparable across the two treatment groups.

Table 3: Baseline Titer Characteristics, ITT Population.

Characteristics	ADV vaccine (N = 3031)	Placebo (N = 1009)	Total (N = 4040)
<u>Type-4 Titer</u>			
Negative*	1906 (63%)	678 (67%)	2584 (64%)
Positive**	1123 (37%)	331 (33%)	1454 (36%)
N	3029	1009	4038
Mean (std)	36.0 (109.6)	37.3 (115.1)	36.3 (111.0)
Median	2.00	2.00	2.00
(Min, Max)	(2.00, 2580.0)	(2.00, 1448.0)	(2.00, 2580.0)
<u>Type-7 Titer</u>			
Negative*	1159 (38%)	377 (37%)	1536 (38%)
Positive**	1870 (62%)	632 (63%)	2502 (62%)
N	3029	1009	4038
Mean (std)	83.0 (313.2)	86.7 (207.5)	83.9 (290.4)
Median	10.1	10.1	10.1
(Min, Max)	(2.0, 10321.0)	(2.0, 2048.0)	(2.0, 10321.0)

* Titer value was < 1:4 at visit 0, ** Titer value was ≥ 1:4 at visit 0

Efficacy Results

The proportion of subjects presenting with wild ADV-4 febrile ARD case (56 Days post vaccination) was the primary endpoint. An ADV-4 febrile ARD case was identified if a subject had one or more clinical signs and symptoms of ARD and an oral temperature $\geq 100.5^{\circ}\text{F}$ (38.06°C) and throat culture positive for wild ADV Type-4 infection.

Also, another primary efficacy variable was the proportion of subjects with ADV-7 seroconversion (SCR), which is the development of ADV Type-7 neutralizing antibody at Week 4 (Day 26) after study medication that represented at least a fourfold increase in titer from baseline (visit 0) in a subject whose baseline Type-7 titer was $<1:4$.

To deal with the multiplicity problem, “A step-down procedure for the 2 primary endpoints was used. The Type-4 febrile ARD rate was analyzed first. Only if the criterion for success was met, the analysis of ADV Type-7 seroconversion was then performed.” (*DR-ADV-301 Clinical Study Report, page 56*).

The vaccine efficacy (VE) was defined as $VE=1-P_v/P_c$, where P_v and P_c are the wild ADV-4 febrile ARD attack rates in the vaccine and placebo arms, respectively. The inferential methods and calculations (point estimate and its 95% CI) related to vaccine efficacy were based on exact statistical procedures and were performed by using the commonly available --(b)(4)-- software.

Wild ADV Type-4 ARD Rate.

From Table 4, the ADV-4 febrile ARD attack rate was 0.07% in the vaccine arm compared to 4.76% in the placebo arm, among subjects in the ITT population. This led to a VE point estimate of 0.986 with its 95% CI as (0.952, 0.998). Similar results were obtained from the Per Protocol population as well, with the VE estimate 0.986 (95% CI: 0.951, 0.998). For efficacy declaration, the study pre-specifications required a minimum value of 0.60 for the lower bound of the VE's 95% CI. With that observed lower bound exceeding 0.60 in the study, the efficacy endpoint of the vaccine in terms of the reduction of the wild ADV-4 febrile ARD attack rate is considered to be established.

Table 4: Wild ADV Type-4 Febrile ARD Cases (Day 0-56), Phase 3 Results.

ARD case	Statistic	ITT Population		PPC Population	
		ADV Vaccine (N=3031)	Placebo (N=1009)	ADV Vaccine (N=2855)	Placebo (N=945)
Yes	n (%)	2* (0.07)	48 (4.76)	2 (0.07)	47 (4.97)
No	n (%)	3029 (99.93)	961 (95.24)	2853 (99.93)	898 (95.03)
	RR (95% CI) [§]	0.014 (0.002, 0.048)		0.014 (0.002, 0.049)	
	VE (95% CI) [§]	0.986 (0.952, 0.998)		0.986 (0.951, 0.998)	

*one subject (11755) that met the case definition but had non-vaccine serotype (B3) is included for conservative estimation of vaccine efficiency.

[§]VE=1 - P_v/P_p , 2-sided confidence interval, by using exact statistical methods -----(b)(4)-----.

As an additional analysis exploring whether the protective effect of the vaccine is unlikely to take place within the first ten days of vaccination (*DR-ADV-301 Clinical Study Report, page 46*), it was found that one wild ADV-4 febrile ARD case occurred in the vaccine arm (N=3031) within the first ten days of vaccination, compared to 4 such cases in the placebo arm (N=1009). This showed a risk reduction ($P_v - P_c$) of 0.0036 (95% CI: 0.0005, 0.0094) among the vaccinees, or a vaccine efficacy of 0.917 with its 95% CI as (0.382, 0.997), using exact statistical methods. This result suggests that the first ten days of vaccination was not completely without any protective effect.

Gender and Age subgroups. Table 5 presents the Wild ADV Type-4 ARD rates (%) in the gender and age subgroups. It is seen that the two ARD cases that occurred in the vaccine arm were males with age ≥ 18 years. The VE estimates (last column) and confidence intervals (based on an exact statistical method) do not suggest any gender or age differences in efficacy. (Note that the numbers in the <18 year-old group were small for precise estimation, thus yielding a wider CI and decreased lower bound, 0.288, compared to the other subgroups). In an exact logistic regression predicting the ARD risk based on the treatment and demographic subgroups, the gender (OR=1.66, 95% CI: 0.85-3.45, P=0.1529) and age (OR=0.71, 95% CI: 0.22-3.70, P=0.7601) differences were not significant.

Table 5: Wild ADV-4 Febrile ARD Rate in Gender and Age Subgroups, Phase 3 Results, ITT Population.

	ADV vaccine (N=3031)	Placebo (N=1009)	VE (95% CI) [§]
Gender			
Male	n=(1910)	(n=642)	
ADV-4 Febrile ARD case	2 (0.10%)	35 (5.45%)	0.981 (0.932, 0.997)
Female	(n=1121)	(n=367)	
ADV-4 Febrile ARD case	0 (0.00%)	13 (3.54%)	1.000 (0.913, 1.000)
Age (yrs)			
< 18	(n=93)	(n=45)	
ADV-4 Febrile ARD case	0 (0.00%)	3 (6.67%)	1.000 (0.288, 1.000)
≥ 18	(n=2938)	(n=964)	
ADV-4 Febrile ARD case	2 (0.07%)	45 (4.67%)	0.985 (0.949, 0.998)

[§] VE=1- P_v/P_p , confidence interval, based on exact statistical methods -----(b)(4)-----

Seroconversion Rates.

ADV Type-7. The seroconversion rates (SCR) and their comparison between arms are provided in Table 6. Considering the assessment for the ADV Type-7 first, as it was one of the primary efficacy variables, the SCRs in the vaccine and placebo arms were respectively 93.8% (95% CI: 92.3%, 95.2%) and 5.3% (95% CI: 3.2%, 8.1%). For efficacy declaration, the lower bound of the 95% CI on the SCR needed to exceed 70%. This condition has been satisfied, with the observed lower bound being 92.3% $>$ 70%, thus establishing that the vaccine's ADV Type-7 seroconversion rate met the required efficacy endpoint.

ADV Type-4. Table 6 also shows that, for ADV Type-4, which is a secondary endpoint, the vaccine demonstrated a considerably high level of seroconversion, with the rate being 94.5% (95% CI: 93.3%, 95.5%), compared to 10.6% (95% CI: 8.3%, 13.2%) in the placebo arm.

Table 6: Seroconversion Rate (SCR), Phase 3 Results.

Seroconversion	Statistic	ADV Type-4		ADV Type-7	
		ADV Vaccine (N=1841)	Placebo (N=653)	ADV Vaccine (N=1120)	Placebo (N=359)
Yes	n (%)	1739 (94.5)	69 (10.6)	1051 (93.8)	19 (5.3)
No	n (%)	102 (5.5)	584 (89.4)	69 (6.2)	340 (94.7)
	95% CI [§] for SCR	(93.3, 95.5)	(8.3, 13.2)	(92.3, 95.2)	(3.2, 8.1)

[§] 2-sided confidence intervals obtained by using exact statistical methods -----(b)(4)-----

Table 7: Wild ADV Type-4 ARD rates (Febrile and Afebrile, Day 0-56), Phase 3 Results, ITT Population.

ARD-4 case	Statistic	ADV Vaccine (N=3031)	Placebo (N=1009)
Yes	n (%)	3 (0.10)	63 (6.24)
No	n (%)	3028 (99.90)	946 (93.76)
	VE (95% CI) [§]	0.984 (0.955, 0.996)	

[§] $VE = 1 - P_v/P_p$, 2-sided confidence interval, based on exact statistical methods -----(b)(4)-----

As another secondary endpoint, all wild ADV Type-4 ARD cases (Day 0-56), febrile and afebrile, were analyzed. A total of 66 such cases occurred, with 3 cases being in the vaccine arm and 63 cases in the Placebo arm (Table 7). This led to a VE estimate of 0.984 with 95% CI: (0.955, 0.996). Regardless of the cases being febrile or afebrile, the VE confidence lower bound exceeded the pre-specified threshold of 0.60.

Lot Consistency Analysis

The objective of assessing the clinical consistency of three manufacturing lots of the vaccine was based on the ADV-4 Titer at Day 26. The pre-specified criterion for clinical consistency required that the 95% CIs on GMT ratios in lot comparisons be contained between $\frac{1}{2}$ and 2. Also, the overall assessment of the consistency was based on more than 80% power, with each pair-wise comparison of lots being powered at more than 93% and with random allocation of 800 subjects per lot.

Table 8 provides the mean and standard deviation (std) of log_eTiter for individual lot. The values for mean±std were 4.46±1.49, 4.56±1.41, and 4.61±1.37 in the three lots, 1, 2, and 3 respectively. The GMT (95% CI) ratios for the comparison between lots 1 and 2, 1 and 3, and 2 and 3 were respectively 0.92 (0.79, 1.08), 0.87 (0.75, 1.02), and 0.94 (0.81, 1.10). As required

by the pre-specified criterion for consistency, the 95% confidence interval in each comparison was contained within $\frac{1}{2}$ and 2.0, thus demonstrating that the manufacturing lots were consistent in ADV-4 titer. This same analysis was carried out for ADV-7 titer as well and the results are presented in Table 9. In all pair-wise comparisons of the three lots, the 95% CIs of the GMT ratios for ADV-7 titer were included within the pre-specified interval ($\frac{1}{2}$, 2), supporting the lot consistency in terms of the ADV-7 titer as well.

Table 8. Mean log_eTiter for ADV Type-4 at Day 26 and GMT Ratios, by Vaccine Lots, Phase 3 Results.

	N	Estimate
log_eGMT±Std:		
Lot 1	759	4.46±1.49
Lot 2	763	4.56±1.41
Lot 3	763	4.61±1.37
GMT Ratio[§]:		
Lot 1 / Lot 2		0.92 (0.79, 1.08)
Lot 1 / Lot 3		0.87 (0.75, 1.02)
Lot 2 / Lot 3		0.94 (0.81, 1.10)

[§] adjusting for effects associated with sites (sitenum) and baseline titer (t4v0).

Table 9. Mean log_eTiter for ADV Type-7 at Day 26 and GMT Ratios, by Vaccine Lots, Phase 3 Results.

	N	Estimate
log_eGMT±Std:		
Lot 1	759	5.27±1.52
Lot 2	763	5.33±1.49
Lot 3	763	5.45±1.36
GMT Ratio (95% CI)[§]:		
Lot 1 / Lot 2		0.95 (0.80, 1.13)
Lot 1 / Lot 3		0.84 (0.70, 0.99)
Lot 2 / Lot 3		0.88 (0.74, 1.05)

[§] adjusting for effects associated with sites (sitenum) and baseline titer (t4v0).

Safety

Table 10 presents an overview of the safety data. There was no report of death, nor were there any reports of AEs contributing to discontinuation in the study. A total of 47 subjects, 35 (1.2%) in the vaccine arm and 12 (1.2%) in the placebo arm, had serious AEs, but no difference in rates across the arms was evidenced (95% CI on the rate difference: (-1.0%, +1.0%). Also, 2703 (89.2%) subjects receiving the vaccine reported treatment-related (i.e., "possibly related," "likely related," or "definitely related") AEs compared to 931 (92.2%) such subjects in the placebo arm, and it appeared that the vaccine had a lower rate of such AEs (95% CI on the rate difference: (-5.0, -1.0). Similar was the case with any treatment emergent AEs, with the rates being about 92.2% in the vaccine arm and 94.2% in the placebo arm (95% CI on the rate difference: (-3.6, -0.1)). In addition, 70.5% of the subjects in the vaccine arm had AEs that required medications

compared to 73.3% in the placebo arm, but the percentages seeking medication did not differ across the arms (95% CI on the difference: (-6.0, +0.4)). Overall, the general safety profile in the vaccine arm was no worse compared to the placebo recipients.

Table 10. Overview of Adverse Events, Safety Population.

	Vaccine (N=3031)		Placebo (N=1009)		95% CI for Vaccine - Plac. (%)	Total (N=4040)	
	n	%	n	%		n	%
# subjects with any Trt emergent AE ¹	2795	92.2	950	94.2	(-3.6, -0.1) ^a	3745	92.7
# Trt emergent AE ¹	13261		4584			17845	
# subjects with any SAEs	35	1.2	12	1.2	(-1.0, +1.0) ^c	47	1.2
# SAEs	42		15			57	
# subjects with Trt related AEs ²	2703	89.2	931	92.2	(-5.0, -1.0) ^a	3634	90.0
# subjects discontinued due to AE	0		0	-	-	0	-
# deaths	0		0	-	-	0	-
# AEs requiring medications ³	5173		1874	-		7049	
# subjects with AEs requiring medications ³	2136	70.5	740	73.3	(-6.0, +0.4) ^a	2877	71.2

¹AE_DRE≥ 2, ²AE_DRE≥ 3, ³AT_MED=1 (per applicant's data dictionary for AE file)

^a asymptotic method, ^c exact statistical method

REVIEWER'S COMMENTS

Efficacy.

Wild ADV-4 Febrile ARD Rate (Day 0-56). The submission data showed that the experimental vaccine met the efficacy endpoint in terms of the reduction of the wild ADV Type 4 febrile ARD attack rate. With 99.93% of subjects having no ARD attack due to wild ADV Type-4 infection during 56 days of experimental vaccination, compared to 95.24% of such subjects among those who received placebo, the experimental vaccine demonstrated a vaccine efficacy of 0.986 with its 95% CI as (0.952, 0.998). The 95% CI lower bound exceeded the pre-specified level of 0.60, and thus established efficacy (ref. Table 4).

Seroconversion Rates (Day 0-26).

ADV Type-7. The ADV Type-7 seroconversion occurred with a rate of 93.8% with its 95% CI: (92.3%, 95.2%) among those who received the vaccine. In comparison, the rate in the placebo arm was 5.3% (95% CI: 3.2%, 8.1%). The ADV Type-7 SCR's 95% CI lower bound exceeded the pre-specified threshold of 70%, thereby establishing efficacy in terms of the vaccine's ADV Type-7 seroconversion rate (ref. Table 6).

ADV Type-4. Although a secondary endpoint, the efficacy in terms of the ADV Type-4 seroconversion as well was demonstrated by the vaccine. The observed seroconversion rate in the vaccine arm was 94.5% (95% CI: 93.3%, 95.5%), compared with only 10.6% (95% CI: 8.3%,13.2%) in the placebo arm (ref. Table 6).

Lot Consistency

The assessment of clinical consistency of the vaccine's three manufacturing lots was based on the ADV-4 Titer at Day 26 (Table 8). The consistency criterion was met in all of the three lots, i.e., the two-sided 95% CIs on GMT ratios in lot pairs excluded both a ½-fold decrease and a 2-fold increase, the bounds that were pre-specified for establishing lot consistency. Similar consistency was concluded based on the ADV-7 titer (at Day 26) as well, where from Table 9, the GMT ratios in lot pairs were included within the pre-specified interval ($\frac{1}{2}$, 2).

Safety

From an overview of the safety data (Table 10), no death attributable to the study vaccine occurred during the trial. The incidence of any serious AEs was 1.2% in both arms, with no significant difference between them (95% CI on the rate difference: -1.0%, +1.0%). The rate of treatment emergent AEs in the vaccine arm seemed to be lower than in the placebo arm, with the 95% CI on the rate difference being (-3.6%, -0.1%). Similar lower rate for the vaccine was noted for the treatment related AEs, with a 95% CI of the rate difference being (-5.0%, -1.0%). Also, about 71.2% of subjects, overall, had AEs requiring medications, but the rate did not differ across the arms (95% CI on the rate difference: -6.0%, +0.4%). Based on these results on the general safety profile of the vaccine relative to placebo, no safety signal of concern was detected.