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Subject: Clinical Review of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral
Enteric Coated Tablets Biologics License Application

To: BLA STN 125296/0

Through: Douglas Pratt, M.D.
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1. General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA#
125296

1.1.2 Related IND
IND (b)(4): Adenovirus Types 4 and & 7 (WI-38 cells) Vaccine, Live, Oral
Tablets

1.1.3 Reviewer Name, Division, and Mail Code
Lewis K. Schrage, M.D.
Division of Vaccines and Related Products Applications
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1.1.4 Submission Received by FDA
30-September-2008

1.2 Product
Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

1.2.1 Proper Name
Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

1.2.2 Trade Name
Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

1.2.3 Product Formulation

Adenovirus Tablet, Type 4 is a white to off-white, round, coated, unscored, biconvex tablet with b4 imprinted on one side. The other side of the tablet is plain. The theoretical weight is ---(b)(4)----.

Adenovirus Tablet, Type 7 is a light peach, round, coated, unscored, biconvex tablet with b7 imprinted on one side. The other side of the tablet is plain. The theoretical weight is --(b)(4)----.

Each Adenovirus Tablet, Type 4 contains approximately (b)(4) of Formulated Adenovirus Type 4 lyophilized virus (drug substance). The unit formula is presented in Table 1.

Table 1: Composition of Adenovirus Tablet, Type 4

Tablet Layer - Component	Quantity (mg/unit)	Reference to Standards
Inner Core - Formulated Adenovirus Type 4 Lyophilized Virus	(b)(4)	Barr Specification
Inner Core - Anhydrous Lactose	-(b)(4)-	NF
Inner Core - Microcrystalline Cellulose	-(b)(4)-	NF
Inner Core - Polacrillin Potassium	-(b)(4)-	NF
Inner Core - Magnesium Stearate	-(b)(4)-	NF
Outer Tablet - Anhydrous Lactose	-(b)(4)-	NF
Outer Tablet - Microcrystalline Cellulose	-(b)(4)-	NF
Outer Tablet - Magnesium Stearate	-(b)(4)-	NF
Enteric Coating Solution - Cellulose Acetate Phthalate	(b)(4)	NF
Enteric Coating Solution - Castor Oil	(b)(4)	(b)(4)
Enteric Coating Solution - Acetone	*	NF
Enteric Coating Solution - Alcohol -- (b)(4)-----	*	(b)(4)
Imprinting - Fine Black Ink --(b)(4)--	*	NA

* Acetone, Alcohol ----(b)(4)----- and Fine Black Ink --(b)(4)-- dissipate during manufacturing and a negligible amount remains in finished product.

NF = Nonformulary; -----(b)(4)----- NA = Not applicable

From Table 1, BLA Section 2.3.P.1, Page 1.

Each Adenovirus Tablet, Type 7 contains approximately (b)(4) of Formulated Adenovirus Type 7 lyophilized virus (Drug Substance). The unit formula is presented in Table 2.

Table 2: Composition of Adenovirus Tablet, Type 7

Tablet Layer - Component	Quantity (mg/unit)	Reference to Standards
Inner Core - Formulated Adenovirus Type 7 Lyophilized Virus	(b)(4)	Barr Specification
Inner Core - Anhydrous Lactose	-(b)(4)-	NF
Inner Core - Microcrystalline Cellulose	-(b)(4)-	NF
Inner Core - Polacrillin Potassium	-(b)(4)-	NF
Inner Core - Magnesium Stearate	-(b)(4)-	NF
Outer Tablet - Anhydrous Lactose	-(b)(4)-	NF
Outer Tablet - Microcrystalline Cellulose	-(b)(4)-	NF
Outer Tablet - FD&C Yellow #6 Aluminum Lake ----- (b)(4) -----	-(b)(4)-	NF
Outer Tablet - Magnesium Stearate	-(b)(4)-	NF
Enteric Coating Solution - Cellulose Acetate Phthalate	(b)(4)	NF
Enteric Coating Solution - Castor Oil	(b)(4)	(b)(4)
Enteric Coating Solution - Acetone	*	NF
Enteric Coating Solution - Alcohol ----- (b)(4) -----	*	(b)(4)
Imprinting - Fine Black Ink --(b)(4)--	*	NA

NF = nonformulary; -----(b)(4)----- NA = Not applicable

Reproduced from Table 2, BLA Section 2.3.P.1, page 2

1.3 Applicant

Teva Women’s Health, Inc.

1.4 Pharmacologic Class

Vaccine

1.5 Proposed Indication

Indicated for active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus Type 4 and Type 7. Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is approved for use in military populations 17 through 50 years of age.

1.6 Dosage Forms and Routes of Administration

Adenovirus Type 4 and Type 7 Vaccine, Live, Oral consists of two enteric coated tablets containing live, wild-type Adenovirus 4 and 7, respectively, for simultaneous oral administration.

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3. Executive Summary

With this BLA, Teva Women's Health, Inc. is seeking approval of their live adenovirus type 4 and adenovirus type 7 vaccine, administered as a single, oral dose, to prevent febrile acute respiratory disease (ARD) due to these adenovirus types in military recruits. The proposed name for the vaccine is Adenovirus Type 4 and Type 7 Vaccine, Live, Oral. The formulations of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral ("ADV 4/7 Vaccine") are provided in Tables 1 and 2.

ARD due to adenovirus type 4 (ADV-4) and adenovirus type 7 (ADV-7) is a common and widespread clinical syndrome occurring among military recruits. In light of the high cost of disease caused by ADV-4 and ADV-7 among military recruits, both on the health of military personnel and the effect of these widespread disease outbreaks on military resources, effective live vaccines for ADV-4 and ADV-7 were developed in the late 1960's and early 1970's. These vaccines consisted of live ADV-4 and ADV-7 grown in human diploid cells and administered in enteric-coated tablets. These wild-type viruses contained in the vaccine were thought to selectively infect the lower intestinal tract while bypassing the respiratory tract. This type of infection usually is asymptomatic and stimulates the development of serum neutralizing antibody to these adenovirus serotypes. At that time, these vaccines were manufactured by Wyeth Laboratories, under contract with the National Institute of Allergy and Infectious Diseases (NIAID) and the Department of the Army under multiple Investigational New Drug applications (INDs). Wyeth Laboratories, Inc. (herein Wyeth) applied for licensure for the ADV-4 vaccine in 1967 and the ADV-7 vaccine in 1974. Starting in the early 1970s, these vaccines were administered to male recruits, during the peak ADV respiratory disease months each year. The FDA approved use of the ADV-4 and ADV-7 vaccines for use in all military personnel on June 20, 1980. The vaccines were administered to female recruits only after a negative pregnancy test was obtained; there were no data regarding the safety of this vaccine in pregnant women. Beginning in 1983, the Army, Navy, and Marines administered both vaccines to basic trainees on a year-round basis. This practice resulted in the effective control of ADV-associated disease in recruit populations.

In 1996, Wyeth the sole manufacturer, made a corporate decision to cease production of the vaccines. By 1999, all existing ADV-4 and ADV-7 vaccine supplies were completely depleted. The halt in vaccine production in 1996 resulted in a resurgence of ADV-induced respiratory illnesses among military recruits undergoing basic training in the U.S. Because of concerns regarding the resurgence of ADV-4 and ADV-7 -related ARD, the Department of Defense (DoD) contracted Barr Pharmaceuticals Inc. (now Teva Women's Health, Inc., a subsidiary of Teva Pharmaceuticals, Inc.) to re-manufacture and re-license these vaccines to vaccinate this at-risk population.

Two clinical studies were conducted to evaluate the safety and efficacy of the applicant's ADV-4 and ADV-7 vaccines in preventing ARD in military recruits. The first, Study BR-ADV-101, a Phase 1, randomized, double-blinded, placebo-controlled study of the safety and immunogenicity of the ADV-4 and ADV-7 vaccines, was conducted in 58 subjects, 30 randomized to receive the vaccines and 28 randomized to receive placebos.

Vaccine virus was not detected in the throat of any subject and no viremia was reported. The observed seroconversion rate at Day 28 was 72.7% (8 of 11 subjects) for the ADV-4 vaccine and 62.5% (10 of 16 subjects) for the ADV-7 vaccine. Overall rates of seroconversion up to and including Day 56 were 81.8% (9 of 11 subjects) for the ADV-4 vaccine and 70.6% (12 of 17 subjects) for the ADV-7 vaccine. Throat and fecal shedding of ADV-4 and ADV-7 vaccine strains also was investigated in the Phase 1 study. Throat swab specimens were collected from all treated subjects enrolled in the Phase 1 study at Study Days 0, 7, 14, 21, 28 and 56 and were tested for the presence of adenovirus. No vaccine virus was detected in the throat swab specimens from any treated subjects. Fecal cultures for adenovirus types 4 and 7 also were obtained on Study Days 0, 7, 14, 21, 28 and 56. Fecal ADV-4 and ADV-7 shedding was observed as early as Day 7. No fecal adenovirus shedding was detectable by Day 28 after vaccination. Overall 8 of 30 (27%) subjects in the vaccine group tested positive at least once for ADV-4 fecal shedding from Day 0 to Day 56. Among the 30 ADV-7 vaccine recipients, 18 (60%) were positive at least once for ADV-7 fecal viral shedding over the entire study period.

The second study, Study DR-ADV-301, was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study in military recruits to evaluate the safety and efficacy of oral ADV-4 vaccine to prevent wild ADV-4-associated ARD and of oral ADV-7 vaccine to induce neutralizing antibody to ADV-7. Subjects were randomized to either the vaccine group or placebo group in a 3:1 ratio. A total of 4041 subjects were randomized and 4040 were analyzed.

The primary endpoints differed for determining the efficacy of the oral ADV-4 and ADV-7 vaccines. Given the relatively low incidence of ARD due to ADV-7 occurring in this population, an evaluation of clinical disease due to ADV-7 as an endpoint was considered not feasible. The primary endpoint for the oral ADV-4 vaccine was the reduction of attack rate of ADV-4 febrile ARD cases in the vaccine recipients compared to placebo recipients, defined as a subject with one or more clinical signs and symptoms of ARD, an oral temperature $> 100.5^{\circ}\text{F}$, and throat culture positive for wild ADV-4 infection. The primary endpoint for the oral ADV-7 vaccine was the rate of ADV-7 seroconversion in the vaccine group, defined as the development of ADV-7 neutralizing antibody at Day 26 after vaccination of at least 1:8 among those subjects whose baseline (Visit 0) ADV-7 titer was $< 1:4$ (the limit of detection of the assay used). For the ADV-4 vaccine, the goal of the analysis of efficacy was to demonstrate a vaccine efficacy (VE) of at least 80% with a lower 95% confidence bound of at least 60%. For the ADV-7 vaccine, the goal of the analysis of efficacy was to demonstrate a seroconversion rate of at least 75% with a lower bound of a 2-sided 95% confidence interval of at least 70%.

Among the 3031 recipients of the ADV-4 vaccine, one developed ARD. The VE estimate of 99.3% was greater than the prespecified success criterion of 80%, and the lower bound of the 95% confidence interval (CI) of 96.0% for VE was greater than 60% for the Intention To Treat (ITT) cohort, allowing one to conclude that the ADV 4/7 Vaccine is superior to the placebo and efficacious in reducing wild ADV-4 febrile ARD cases. Additionally, the ADV-7 seroconversion rate (93.8%) for the vaccine group is greater than 75% and the lower bound of the 2-sided 95% CI (92.4%) is greater than 70%, allowing one to conclude that the ADV 4/7 Vaccine is effective with respect to ADV-7 seroconversion.

Consistency of manufacture also was evaluated in the Phase 3 study by comparing Geometric Mean Titer (GMT) among three manufacturing scale lots. For ADV-4, the 95% CIs for the GMT ratios Lot1/Lot2, Lot2/Lot3, and Lot1/Lot3 were (0.79, 1.05), (0.82, 1.09), and (0.75, 0.99), respectively. All were within the pre-specified boundaries of (0.50, 2.00), permitting a conclusion that the antibody responses induced by each of the three vaccine lots were equivalent with respect to ADV-4 titer. For ADV-7, the 95% CIs for the GMT ratios Lot1/Lot2, Lot2/Lot3, and Lot1/Lot3 were (0.81, 1.09), (0.77, 1.03), and (0.72, 0.97) respectively. All were within the boundaries of (0.50, 2.00), permitting a conclusion that the three vaccine lots were equivalent with respect to ADV-7 titer. Taken together, these data provide clinical evidence supporting the consistency of manufacture.

A total of 3,733 (92.40%) subjects reported 17,654 treatment-emergent adverse events. A total of 47 (1.16%) subjects reported 57 serious adverse events. Overall, the rates of adverse events and serious adverse events were comparable between the two treatment groups. A total of 3,527 (87.30%) subjects reported one or more cases of treatment-related adverse events, where treatment-related adverse events were the treatment-emergent events possibly, likely or definitely related to the study medication (as determined by investigational site personnel). Treatment-emergent adverse events were the events that started on or after the vaccination date (Day 0). The incidences of treatment-related adverse events were comparable between the two treatment groups. Most common treatment-related adverse events were upper respiratory tract infection and headache.

No deaths were reported among study subjects in either the Phase 1 or Phase 3 studies during the study period. No subject discontinued participation in either the Phase 1 or Phase 3 studies due to adverse events.

A total of five pregnancies (four in the vaccine group and one in the placebo group) were reported during the Phase 3 study. Among the pregnancies in the vaccine group, three subjects were estimated to have conceived two to thirteen days prior to vaccination. One subject (Subject 11580) conceived approximately twenty-one weeks after she was vaccinated. All four pregnant subjects assigned to the vaccines arm delivered healthy infants at estimated gestational ages between 36 4/7 and 39 5/7 weeks. Teva Women's Health, Inc. is requesting a waiver of the pregnancy labeling regulations as no pregnancy category fits the teratogenicity criteria as specified in 21 CFR 201.57(c)(9)(i)(A).

Because a risk benefit assessment, based upon literature reports of fetal harm due to adenovirus infection with unspecified serotypes and the intended use of this vaccine primarily among military recruits, does not support the use of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in pregnant women, the requested pregnancy category will be as follows: Pregnancy Category: Contraindicated.

The proposed dosing regimen is to administer the ADV-4/7 Vaccine as a one-time, oral vaccine, consisting of one tablet containing ADV-4 and one tablet containing ADV-7. The vaccine is intended for military populations in which the epidemic ARD due to ADV-4 and ADV-7 have been shown to occur.

Drug-drug and drug-disease interactions were not assessed.

Special populations: As this product is intended for the exclusive use in U.S. military recruit populations, CBER recommends a waiver of PREA requirements for assessments of safety and efficacy in pediatric populations 0 through 17 years of age.

Medical reviewer note regarding Vaccines and Related Biological Products Advisory Committee (VRBPAC) review: VRBPAC review of the licensure decision for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral was not deemed necessary by CBER based on the high degree of efficacy and safety demonstrated in the definitive Phase 3 study and the limited population for which this product is indicated.

Postmarketing - Risk Management Plans

The postmarketing plans, subject to reporting requirements of 21 CFR 601.70, as specified by Dr. Wei Hua, the epidemiological safety reviewer from the Office of Biostatistics and Epidemiology, and agreed to by Teva Women's Health, Inc., are as follows:

1. To conduct a postmarketing sentinel surveillance study to detect potential safety signals and to monitor and analyze uncommon and unexpected medical events occurring within 42 days following vaccination in the first 100,000 military recruits exposed to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, during the first year post-approval through the use of the Defense Medical Surveillance System (DMSS). The final study report will be submitted by January 31, 2013.

Final protocol submission date: September 13, 2010
Study/trial completion date: July 31, 2012
Final Report Submission date: January 31, 2013

2. To conduct a prospective Pregnancy Registry study of pregnant women exposed to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, and their live born offspring through the first year of life to detect potential safety signals. Approximately 340 live births are anticipated to be enrolled in an estimate of 2-4 years. The Pregnancy Registry Status Report will be submitted to CBER annually. The final study report will be submitted 6 months after the follow-up of the last subject is completed and no later than March 31, 2017.

Final protocol submission date: September 13, 2010
Study/trial completion date: September 30, 2016
Final Report Submission date: March 31, 2017

3. To conduct a surveillance study for vaccine-associated febrile respiratory illness (FRI) due to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, viral shedding. Vaccine viral shedding will be evaluated using data from the Naval Health Research Center (NHRC) Febrile Respiratory Illness Surveillance Program. The NHRC FRI data will be reviewed on a monthly basis. The proportion of FRI subjects positive for Adenovirus Type 4 and Type 7 will be evaluated on a quarterly basis and cumulatively throughout the study period to identify if there are upward trends or unusual patterns of adenovirus FRI indicating a potential signal for the transmission of the virus to the respiratory tract, thereby resulting in FRI. This surveillance will be conducted concurrently with the Sentinel Surveillance Plan which covers the first 100,000 recruits exposed to the vaccine during the first year post-approval. The final report will be submitted with the Sentinel Surveillance study final report by January 31, 2013.

Final protocol submission date: September 13, 2010
Study/trial completion date: July 31, 2012
Final Report Submission date: January 31, 2013.

Medical reviewer comment: The medical reviewer finds these post marketing commitment risk management plans generally adequate and acceptable. We will request that the applicant provide to CBER the ADV-4 and ADV-7 surveillance information collected from the FRI on an annual basis.

Medical reviewer recommendation: The safety, efficacy and immunogenicity data included in the BLA support approval of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, as a safe and effective means of preventing or reducing wild febrile and/or afebrile ARD caused by ADV-4, and in inducing neutralizing antibodies to Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in the U.S. military recruit population.

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls

During CBER's pre-approval inspections of the Forest, VA, facility, the applicant was cited for 9 FDA 483 items related to facility, manufacturing, product and quality issues. The responses to the FDA 483 items were received, reviewed and found to be acceptable.

There are no ongoing or pending investigations and no compliance actions with respect to the above facility or its products. Therefore, the Office of Compliance and Biologics Quality does not object to the approval of this submission. The facilities reviewer considers this submission approvable on the basis of the facilities information provided.

The ADV-4 and ADV-7 components of this vaccine are nearly identical to those previously licensed. The same ADV-4 and ADV-7 strains and WI-38 cells as Wyeth had developed and produced for more than thirty years were used in this vaccine. Wyeth transferred to the current applicant the ADV-4 and ADV-7 seeds and various production and testing documents necessary to produce the ADV-4 and ADV-7 drug substances. The key starting materials and manufacturing processes for the drug substances were selected and designed by the applicant to be highly similar to the processes used for the production by Wyeth of the previously licensed ADV-4 and ADV-7 vaccines. The virus strains have not been attenuated or otherwise genetically modified so they are wild-type virus strains with the potential to cause infection and disease. Three minor changes were made to the processing of the drug substance in comparison to the Wyeth process:

- 1) antibiotics were not used in the growth media to make the current vaccine;
- 2)------(b)(4)-----
- 3) -----(b)(4)-----.

A comparison of the Teva and Wyeth manufacturing processes for ADV-4 and ADV-7 drug substances is presented in Table 3.

Table 3: Comparison of the Teva (previously Barr Pharmaceuticals) and Wyeth Manufacturing Processes for Adenovirus Type 4 and Type 7 Drug Substances[†]

Component	Wyeth	Barr	Key Differences	Significance
Cells	Human Diploid Cells (WI-38)	Human Diploid Cells (WI-38)	None	None
Virus	ADV4 CL68578p12	ADV4 CL68578p15	None	None
	ADV7 55142p13	ADV7 55142p16	None	None
Cell Growth Media	EMEM Media + 10% FBS and antibiotics	DMEM Media + 10% FBS	Antibiotics removed	---(b)(4)---
Infection Media	Media + 2% FBS	Media + 2% FBS	None	None
MOI	Estimated 0.1 – 1.0 TCID ₅₀ /cell	0.1 – 0.7 TCID ₅₀ /cell	None	None
Incubation	14 days	10-14 days	None	None
Harvesting	0.8 / 0.45 micron filters	0.8 / 0.45 micron filters	None	None
Stabilizer	10% SPGA	10% SPGA	None	None
Lyophilizer Container	Open Trays	---(b)(4)--- trays	---(b)(4)---	---(b)(4)---

ADV4 = adenovirus type 4; ADV7 = adenovirus type 7; EMEM = Eagle’s Minimal Essential Medium; DMEM = Dulbecco’s Modified Eagle’s Medium; FBS = Fetal Bovine Serum; TCID = Tissue Culture Infectious Dose 50; SPGA = Sucrose, Phosphate, Gluconate, Albumin)

[†]Reproduced from Table 2, BLA Section 3.2.S.1.2, page 3

Each ADV-4 tablet contains approximately -----(b)(4)----- of formulated ADV-4 lyophilized virus (Drug Substance). The unit formula is presented in Table 4.

Table 4: Composition of Adenovirus Tablet, Type 4[†]

Tablet Layer - Component	Quantity (mg/unit)	Reference to Standards
Inner Core - Formulated Adenovirus Type 4 Lyophilized Virus	(b)(4)	Barr Specification
Inner Core - Anhydrous Lactose	-(b)(4)-	NF
Inner Core - Microcrystalline Cellulose	-(b)(4)-	NF
Inner Core - Polacrillin Potassium	-(b)(4)-	NF
Inner Core - Magnesium Stearate	-(b)(4)-	NF
Outer Tablet - Anhydrous Lactose	-(b)(4)-	NF
Outer Tablet - Microcrystalline Cellulose	-(b)(4)-	NF
Outer Tablet - Magnesium Stearate	-(b)(4)-	NF
Enteric Coating Solution - Cellulose Acetate Phthalate	-(b)(4)-	NF
Enteric Coating Solution - Castor Oil	(b)(4)	(b)(4)
Enteric Coating Solution - Acetone	*	NF
Enteric Coating Solution - Alcohol ----- ------(b)(4)-----	*	(b)(4)
Imprinting - Fine Black Ink --(b)(4)--	*	NA

*Acetone, Alcohol -----(b)(4)----- and Fine Black Ink-- (b)(4)-- dissipate during manufacturing and a negligible amount remains in finished product.

NF = Nonformulary; -----(b)(4)----- NA = Not applicable

[†]Reproduced from Table 1, BLA Section 2.3.P.1, page 1

Each ADV-7 tablet contains approximately 10 milligrams of formulated ADV-7 lyophilized virus (Drug Substance). The unit formula is presented in Table 5.

Table 5: Composition of Adenovirus Tablet, Type 7[†]

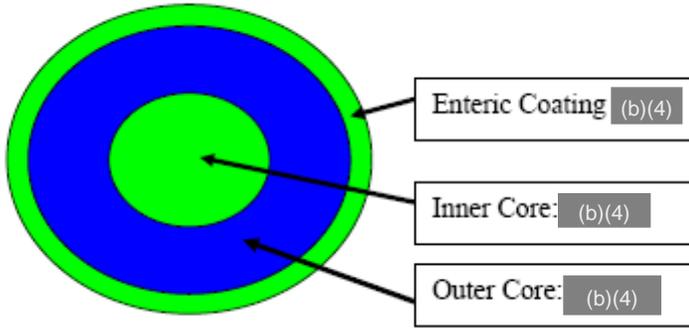
Tablet Layer - Component	Quantity (mg/unit)	Reference to Standards
Inner Core - Formulated Adenovirus Type 7 Lyophilized Virus	-(b)(4)-	Barr Specification
Inner Core - Anhydrous Lactose	-(b)(4)-	NF
Inner Core - Microcrystalline Cellulose	-(b)(4)-	NF
Inner Core - Polacrillin Potassium	-(b)(4)-	NF
Inner Core - Magnesium Stearate	-(b)(4)-	NF
Outer Tablet - Anhydrous Lactose	-(b)(4)-	NF
Outer Tablet - Microcrystalline Cellulose	-(b)(4)-	NF
Outer Tablet - FD&C Yellow #6 Aluminum Lake ------(b)(4)-----	-(b)(4)-	NF
Outer Tablet - Magnesium Stearate	-(b)(4)-	NF
Enteric Coating Solution - Cellulose Acetate Enteric Coating Solution - Phthalate	(b)(4)	NF
Enteric Coating Solution - Castor Oil	(b)(4)	(b)(4)
Enteric Coating Solution - Acetone	*	NF
Enteric Coating Solution - Alcohol -----(b)(4)-----	*	(b)(4)
Imprinting - Fine Black Ink -(b)(4)-	*	NA

NF = Nonformulary; -----(b)(4)----- NA = Not applicable

[†]Reproduced from Table 2, BLA Section 2.3.P.1, page 2

The Adenovirus Tablets, Type 4 and Type 7, consist of the inner core, outer core and the enteric coating dispersion. A schematic of the tablet is shown in Figure 1.

Figure 1: Adenovirus Tablet, Type 4 and 7[†], demonstrating the inner core --(b)(4)-- the outer core --(b)(4)-- and the enteric coating -(b)(4)-.



[†]Reproduced from Figure 1, BLA Section 2.3.P.1, page 3

4.2 Animal Pharmacology/Toxicology

Animal toxicology studies were not required by CBER due to the lack of a validated, biologically relevant animal model for use in evaluating live ADV-4 and ADV-7, and given the extensive clinical experience with the similar Wyeth Adenovirus 4 and Adenovirus 7 vaccines.

4.3 Statistics

The CBER statistician reviewed the data from the pivotal immunogenicity trial, DR-ADV-301. The reviewer came to the following conclusions:

- 1) ADV-4 efficacy: The estimate of vaccine efficacy (0.986) and its 2-sided 95% CI (0.952, 0.998) exceeded the pre-specified thresholds of 0.80 and 0.60, respectively, thereby establishing the vaccine's efficacy endpoint in terms of reduction in wild ADV-4 febrile ARD attack rate.
- 2) ADV-7 efficacy: The observed seroconversion point estimate of 93.8% and its 2-sided 95% CI (92.3%, 95.2%) exceeded the pre-specified thresholds of 75% and 70%, respectively.
- 3) The study results supported the clinical lot consistency criteria for the three manufacturing lots for both ADV-4 and ADV-7 vaccines.
- 4) The ADV 4/7 Vaccine demonstrated a comparable general safety profile with placebo.

4.4 Facilities Review of Request for Categorical Exclusion from the Requirement of an Environmental Assessment

The applicant has sought a claim for Categorical Exclusion from performing an Environmental Assessment pursuant to 21 CFR 25.31(c), claiming that the approval of this application would not significantly alter the concentration or distribution of a substance that occurs naturally in the environment, its metabolites, or degradation products. The bases for this request include the following:

- The human adenovirus strains used in the vaccine are identical to the wild-type adenoviruses that have circulated in the U.S. general population for the past 50 years;
- During bulk production, multiple measures have been put in place to mitigate the risk of virus entering the environment during production;
- The vaccine will only be administered to military recruits at the beginning of basic training. Recruits are isolated from the general public during training for at least five weeks, minimizing the risk that the virus could spread to the general population.

The claim for Categorical Exclusion from Environmental Assessment was accepted by the CBER facilities reviewer.

Medical reviewer comment: I concur with the assessment of the facilities reviewer.

5. Clinical and Regulatory Background

5.1 Diseases to be Prevented and Available Interventions

At least 52 distinct types of adenovirus can cause human infections. Adenoviruses are unusually stable to chemical and physical agents and to adverse pH conditions and can survive outside of the body for prolonged periods. Typing of adenoviruses is most often accomplished by neutralization by specific antisera. Protection from ADV disease is associated with serotype-specific neutralizing antibodies, although protection likely is not mediated solely by neutralizing antibodies.

The ADV 4/7 Vaccine is intended for the prevention of febrile ARD caused by ADV-4 and ADV-7 in U.S. military recruits. The definition for ARD in Army trainees requires a temperature of $\geq 100.5^{\circ}\text{F}$ (38.06°C) with symptoms of respiratory disease. ADV incubation period is typically four to five days, after which illness induced by ADV is characterized by fever $\geq 100.5^{\circ}\text{F}$ (38.06°C), sore throat, nasal congestion, headache, and malaise typically lasting three to five days. Physical examination may reveal pharyngitis, rales, and rhonchi. Approximately seven percent to ten percent of infections are complicated by pneumonitis on chest X-ray. Transmission from person to person is mainly by inhalation of respiratory droplets.

There is no licensed vaccine to prevent ARD due to ADV Type 4 and Type 7 infection.

5.2 Previous Human Experience with Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, and Related Vaccines

A vaccine similar to the ADV 4/7 Vaccine, manufactured by Wyeth, was licensed for use in U.S. military recruits to prevent ARD due to ADV-4 and ADV-7 infection on June 20, 1980. The vaccine was administered to female recruits only after a negative pregnancy test was obtained; there were no data regarding the safety of this vaccine in pregnant women. Beginning in 1983, the Army, Navy, and Marines administered this vaccine to basic trainees, excepting pregnant women, on a year-round basis. This practice resulted in the effective control of ADV-associated disease in recruit populations.

In 1996, Wyeth ceased production of the vaccine following a corporate decision. By 1999, all existing ADV-4 and ADV-7 vaccine supplies were completely depleted. The halt in vaccine production in 1996 resulted in a resurgence of ADV-induced respiratory illnesses among military recruits undergoing basic training in the U.S. Because of concerns regarding the resurgence of ADV-4 and ADV-7 -related ARD, the Department of Defense contracted Barr Pharmaceuticals Inc. (now a component of Teva Women's Health, Inc.) to manufacture and license similar vaccines for this at-risk population.

5.3 Regulatory Background Information

Chronology of Review:

- 30 September 2008: Application Receipt
- 10 October 2008: Committee Assignment
- 20 October 2008: First Committee Meeting
- 07 November 2008: Filing Meeting
- 24 November 2008: Filing Action
- 24 November 2008: No Deficiencies Identified
- 31 July 2009: Action Due Date (original ADD)

6. Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA Files Reviewed

The following files served as the basis for the clinical review:

- Original BLA Submission, 30 September 2008
 - Study BR-ADV-101 Clinical Study Report
 - Study DR-ADV-301 Clinical Study Report
 - Request for Pediatric Waiver
 - DR-5001 Risk Evaluation and Mitigation Strategy
 - Support for Label
- 120 Day Safety Update 1
- BLA Amendment 30, Resubmission to CBER's 16 July 2009 CR Letter

- BLA Amendment 32, Response to CBER's Information Request
- BLA Amendment 35, response to CBER's Information Request
 - Environmental Analysis: Claim for Categorical Exclusion
- BLA Amendment 37, Agreed-upon Postmarketing Commitments

6.1.2 Literature

Brandt CD, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease. I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. *Am J Epi* 1969;90:484-500.

MMWR (CDC). Adenovirus type 7 outbreak in a pediatric chronic care facility – Pennsylvania 1982. 1983;32:258-260.

Gerber SI, et al. Outbreak of adenovirus 7d2 infection in a pediatric chronic care facility and tertiary care hospital. *Clin Infect Dis* 2001;32:694-700.

Mitchell LS, et al. Adenovirus 7a: a community-acquired outbreak in a children's hospital. *Ped Infect Dis Jnl* 2000;19:996-1000.

Wong S, et al. Detection of a broad range of human adenoviruses in respiratory tract samples using a sensitive multiplex real-time PCR assay. *J Med Virol* 2008;80:856-865.

Top, FH, et al. Immunization with live types 7 and 4 adenovirus vaccines. II. Antibody response and protective effect against acute respiratory disease due to adenovirus type 7. *Jnl Infect Dis* 1971;124(2):155-160.

Barraza EM, et al. Reemergence of adenovirus type 4 acute respiratory disease in military trainees: report of an outbreak during a lapse in vaccination. *Jnl Infect Dis* 1999;179:1531-1533.

6.1.3 Postmarketing Experience

Not applicable

6.2 Table of Clinical Studies

Data from the two clinical studies of the applicant's ADV 4/7 Vaccine administered to U.S. military recruits were included in the BLA (Table 6). One of the studies, Study DR-ADV-301, is considered pivotal for the evaluation of the safety and immunogenicity of the ADV 4/7 Vaccine. Study BR-ADV-101 provides supportive safety and immunogenicity data, including shedding data, for the evaluation of the ADV 4/7 Vaccine.

Table 6: Studies Included in the ADV Type 4 and Type 7 Vaccine, Live, Oral, BLA

Study	Groups (ratio)	Total Vaccinated Cohort Planned/Actual (N)
BR-ADV-101	Vaccine/Placebo (1/1)	30/30
DR-ADV-301	Vaccine/Placebo (3/1)	3031/3031

6.3 Review Strategy

The BLA contains the complete clinical study reports for Studies BR-ADV-101 and DR-ADV-301. All of the safety and immunogenicity data provided for the pivotal study, Study DR-ADV-301, and for the supportive study, Study BR-ADV-101, were reviewed.

6.4 Good Clinical Practices and Data Integrity

The Division of Inspections and Surveillance performed bioresearch monitoring inspections of the two clinical sites at which subjects were studied, in support of this BLA. The inspections did not reveal any problems that impact the data submitted in the application.

6.5 Financial Disclosures

On Form 3454, the applicant certified that the following statement is correct:

“As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

7. Human Pharmacology (See Section 8)

8. Clinical Studies

8.1 Pivotal Trial

8.1.1 Applicant’s Protocol Number and Protocol Title

Study DR-ADV-301: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of DR-5001. The ClinicalTrials.gov identifier is NCT00382408.

8.1.1.1 Objective/Rationale

The primary objectives of the study were to determine the efficacy of the oral ADV-4 component of the ADV4/7 Vaccine in reducing the attack rate of wild ADV-4-associated febrile ARD, and to determine the antibody response to the ADV-7 component of the oral ADV 4/7 Vaccine in U.S. military recruits. Secondary objectives were to determine the antibody response to the oral ADV-4 Vaccine component and to evaluate the safety and tolerability of the oral ADV 4/7 Vaccine in U.S. military recruits, and to assess lot consistency among the three manufactured lots of the oral ADV 4/7 Vaccine.

8.1.1.2 Design Overview

This was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study in military recruits. Subjects meeting study criteria were randomized to either the vaccine group or the matching placebo group in a 3:1 ratio. As there were three lots of each vaccine used in this trial, the randomization to different lots among the individuals receiving vaccine was done in blocks of eight.

8.1.1.3 Population

Inclusion Criteria:

- Active duty military recruit age seventeen or older
- Provide written informed consent
- Military recruit in training
- Willing to meet the specimen-collection schedule
- Female subjects must have been of non-childbearing potential, i.e. surgically sterilized, or if of childbearing potential, had a documented negative β HCG pregnancy test \leq 72 hours prior to study medication administration and agreed not to become pregnant and to inform any/all sexual partners that she is potentially infectious for 90 days after the Study Medication Administration Visit (Visit 1). Effective ways to avoid pregnancy include: abstinence, hysterectomy, bilateral oophorectomy, tubal ligation, male condoms, oral contraceptives, or an intrauterine device.
- Male subjects agreed to inform any/all sexual partners that he is potentially infectious and to avoid unprotected sexual intercourse for 90 days after the Study Medication Administration Visit (Visit 1). Effective ways to avoid unprotected sexual intercourse include: abstinence, vasectomy, or male condoms.

Exclusion Criteria:

- If the subject was female, nursing an infant or planning on nursing during the study and/or at anytime during the 90 days after the Study Medication Administration Visit (Visit 1)
- Immunosuppressed for any reason, including past (within last 6 months of study enrollment) or current treatment with systemic immunosuppressive therapy (systemic corticosteroids, chemotherapy or radiation therapy)

- Known allergy to any component of the vaccines and/or placebo tablets (full components of the placebo and active vaccine tablets may include: ADV-4 or ADV-7 virus, monosodium glutamate, sucrose, d-mannose, d-fructose, dextrose, lactose, cellulose, human serum albumin, fetal bovine serum, potassium phosphate, polyvinylpyrrolidone, microcrystalline cellulose, prolacrilin potassium, magnesium stearate, acetate phthalate, FD&C #6 dye, alcohol, acetone, and castor oil.)
- Use of any investigational new or non-registered drug or vaccine other than the study medication planned during the study period or within 30 days preceding the study medication administration; however, subjects were allowed to receive routine vaccinations associated with basic training and any other prescribed medications not in the exclusion criteria
- Unable or unwilling to return for follow-up visits
- If the subject appeared to be too ill for participation in the study as determined by the Principal Investigator, or qualified designee
- Any condition that would make a subject unsuitable for the study as determined by the Principal Investigator or designated qualified sub-investigator
- Immunocompromised sexual partner or presence of immunocompromised individuals (e.g., HIV, recent or current chemotherapy), children under 1 year of age, or pregnant female in home of record

Medical reviewer comment: Although the inclusion criteria set no upper limit on the age of the subjects, the oldest subject to be enrolled was age 42. Additionally, it should be noted that the inclusion criteria restricted participation to active duty military recruits, the population for whom the vaccine is intended.

Concomitant Products:

Ill or injured study subjects could use prescription medications during the study, as prescribed by licensed DoD health care providers and were allowed to receive routine vaccinations associated with basic training.

Military recruits were excluded from participating in this study for use of the following medications:

- Any investigational or non-registered drug or vaccine other than the study medication within 30 days preceding study medication administration;
- Current use, or within previous six months preceding study medication administration, of systemic immunosuppressive therapy (systemic corticosteroids, chemotherapy, or radiation therapy);

8.1.1.4 Products Mandated by the Protocol

Dosage and Administration of Study Vaccines:

This was a one-time dose regimen. All randomized subjects received a single ADV-4 tablet vaccine, and a single ADV-7 tablet vaccine, or matching placebo tablets, at study Visit 1. Vaccine tablets contained live ADV, either Type-4 or Type-7, at an average potency of no less than 32,000 tissue-culture infective doses (4.5 log₁₀ TCID₅₀). Both vaccine tablets and placebo tablets were administered orally, kept in the mouth as briefly

as possible and swallowed whole with water. Chewing the tablets was not permitted. If breakage of the study medication tablets occurred while in the mouth, the subject was provided with water and instructed to rinse and spit out any remaining particles. Tablets were administered simultaneously; however, if the subject was unable or unwilling to swallow both tablets at once, the subject was permitted to take one tablet immediately following the other. Study personnel observed the ingestion and conducted a mouth check on each subject to confirm study drug administration. Subjects were observed for a period of approximately 30 minutes after test product administration and any adverse events were recorded. At Visit 2, subjects were asked if they subsequently vomited any of the pills within 24 hours after study medication administration.

Formulation of Study Vaccines:

Both the ADV-4 and ADV-7 vaccine tablets contain a viable, selected strain of wild Type-4 (CL68578) or Type-7 (55142) ADV, prepared from tissue cultures of human diploid fibroblast cells (WI-38). Each enteric-coated tablet (ECT) contains an inner virus core containing anhydrous lactose, micro crystalline cellulose, polacrillin potassium, magnesium stearate, and live ADV, either Type-4 or Type-7, at an average potency of no less than 32,000 tissue-culture infective doses ($4.5 \log_{10} \text{TCID}_{50}$). (See also Section 1.2.3).

The ADV-4 vaccine tablet is a white to off-white, round, coated unscored, biconvex tablet containing a live strain of wild Type-4 Adenovirus, oral administration. The lots of Type-4 ADV used were as follows: Lot 708486001R, Lot 708486002R, and Lot 708486003R.

The ADV-7 vaccine tablet is a light peach colored, round, coated, unscored, biconvex tablet containing a live strain of wild Type-7 Adenovirus, oral administration. The lots of Type-7 ADV used were as follows: Lot 708496001R, Lot 708486004R, and Lot 708496005R.

Placebo

The placebo tablets were identical to the vaccine tablets but for the absence of ADV-4 (Lot #706446001R) and ADV-7 (Lot #706456001R), respectively.

8.1.1.5 Endpoints

8.1.1.5.1 Primary Efficacy Endpoints

The primary efficacy endpoint for the evaluation of ADV-4 vaccine efficacy was the development of an ADV-4 febrile ARD case, defined as a subject with one or more clinical signs and symptoms of ARD (mild to severe respiratory symptoms of one or more of the following: sore throat, cough, rhinorrhea or nasal congestion), an oral temperature $\geq 100.5^{\circ}\text{F}$ (38.06°C), and throat culture positive for wild ADV-4 infection. This definition is identical to the one proposed in the final Phase 3 protocol, dated 29 March 2006.

For the oral ADV-4 vaccine, the attack rate of the febrile ADV-4-associated ARD cases observed among subjects in the vaccine group and placebo group from the day of study medication administration (Day 0) to the final study visit (Day 56) was calculated. The vaccine efficacy (VE) was defined as: $VE = 1 - R$, where $R = P_{(vaccine)}/P_{(placebo)}$ was the relative risk of ARD attack in subjects who received vaccines compared to placebos. An additional analysis excluding those ARD cases occurring within the first 10 days following study medication administration also was conducted because the protective effect of the vaccine was unlikely to take place within 10 days of vaccine administration.

The primary efficacy variable for the evaluation of ADV-7 vaccine efficacy was ADV-7 seroconversion, defined as the development of ADV-7 neutralizing antibody at Week 4 (Day 26) after receiving study vaccine that was at least a fourfold increase in titer from baseline (visit 0) in a subject whose baseline Type-7 titer was <1:4. By convention, titers <1:4 were assigned a value of 1:2. Accordingly, a Week 4 (Day 26) titer was required to be at least 1:8 for a determination that seroconversion had occurred. For the oral ADV-7 vaccine, seroconversion rates observed at Week 4 (Day 26) for the oral ADV-7 vaccine and placebo groups were calculated and the 95% confidence intervals were obtained based on the normal approximation for the confidence interval for a proportion.

Medical reviewer comment: The actual definition of seroconversion provided in the BLA was “the development of ADV Type–7 neutralizing antibody at Day 26 after vaccination of at least a fourfold increase in titer from baseline (Visit 0) in subjects whose baseline ADV Type-7 titer was <1:4.” In an information request to the applicant in which CBER sought clarification of this definition, the applicant confirmed that, in practice, subjects whose baseline ADV-7 titers were <1:4 were assigned a value of 1:2 by convention (BLA Amendment 32, 16 December 2010). As a fourfold increase in titer would be represented by a titer of 1:8, this value was selected as the definition of seroconversion, an approach to defining seroconversion that CBER considered appropriate and acceptable.

The ADV-7-related endpoint was immunological—the development of anti-ADV-7 neutralizing antibodies—due to the low incidence of ADV-7 disease occurring among U.S. military recruits at the time when this Phase 3 study was conducted. In an earlier trial, rates of hospitalization due to ADV-7-associated ARD were compared among military recruits receiving the Wyeth ADV-4 vaccine administered with a placebo (control group) and recruits receiving ADV-4 vaccine in combination with ADV-7 vaccine. ARD hospitalizations associated with ADV-7 occurred in 123 (13.4%) of 920 men in the control group, while only one (0.4%) of 231 receiving both ADV-4 and ADV-7 vaccines were hospitalized with ADV-7 ARD. An immunogenicity substudy revealed that, among men vaccinated with both ADV-4 and ADV-7 vaccines, 20 (86%) of 23 men tested developed neutralizing antibody to ADV-7, while in the control group, where no ADV-7 vaccine was given, only two (10%) of 21 men tested developed ADV-7 neutralizing antibodies.

Serotyping of ADV isolates from throat specimens was performed at the -----(b)(4)-----
----- Isolates were detected by evidence of cytopathic effect (CPE)
from throat swab specimens inoculated using a continuous cell line of -----
----- (b)(4) ----- cells which supports the growth of ADV. Cell cultures
exhibiting 3-4+ CPE during incubation were harvested and stained by -----
----- (b)(4) ----- technique using ADV monoclonal antibody (b)(4). If the specimen
was found to be (b)(4) positive for ADV, the isolate was sent to the (b)(4) molecular
biological laboratory for serotyping. No further testing was performed on (b)(4)-negative
specimens.

A PCR-based assay, developed by the -(b)(4)- was used to further identify the serotype
designation of adenoviruses isolated from patient samples, with the goal being to identify
vaccine strain virus from wild-type virus in patients diagnosed with acute respiratory
disease (ARD). Vaccine strains included Species E, serotype 4, genome type 4p1 and
Species B, serotype 7a. Samples were first tested for the presence of DNA from
adenovirus species B, C and E. If samples were positive for 4a, results were reported
positive for Field Strain Ad4a. If samples were positive for 4p, samples were further
tested using the Walter Reed Army Institute of Research Ad4p1 vs. Ad4p3 PCR test.
This test was used to distinguish Ad4p1 (vaccine) from Ad4p3 (circulating field strain).
If samples were positive for Ad4p1, results were reported as Vaccine strain. If samples
were positive for Ad4p3, results were reported as Field Strain Ad4p3.

Samples positive for adenovirus Species B were tested for specific administration of
ADV types 3, 7 and 21 using a multiplex PCR. If samples were positive for ADV-7,
sequencing was performed to determine if they were field or vaccine strains. If the
samples were sequenced for Ad7a, the results were reported as Vaccine Strain. Isolates
positive for any other adenovirus strain B, except for type 7, were reported as Field Strain
B. Samples positive for adenovirus strain C isolates were reported as Field Strain
adenovirus C. No further testing was performed in these isolates.

For the Type-4 vaccine, the goal of the analysis of efficacy was to demonstrate a vaccine
efficacy of at least 80% with a lower 95% confidence bound at least 60%. For the Type-7
vaccine, the goal of the analysis of efficacy was to demonstrate a seroconversion rate of
at least 75% with a lower bound of a 2-sided 95% confidence interval of at least 70%.

8.1.1.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints to support evaluation of the efficacy of the ADV-4 vaccine were:

- ADV-4 seroconversion: defined as the development of ADV-4 neutralizing antibody at Week 4 (Day 26) after study vaccine that was at least a fourfold increase in titer from baseline (Visit 0) in a subject whose baseline ADV-4 titer was $<1:4$.
- ADV-4 ARD case regardless of whether the subject was febrile or not: a subject with one or more clinical signs and symptoms of ARD and throat culture positive for wild ADV-4 infection and who was too ill to perform normal training duties.
- ADV-4 booster effect: defined as the development of ADV-4 neutralizing antibody at Week 4 (Day 26) that was at least a fourfold increase in titer from baseline (Visit 0) in a subject whose baseline ADV-4 titer was $\geq 1:4$.

Medical reviewer comment: As noted previously, the applicant later confirmed that, in practice, subjects whose baseline ADV-4 or ADV-7 titers were $<1:4$ were assigned a value of $1:2$ by convention (BLA Amendment 32, 16 December 2010). As a fourfold increase in titer would be represented by a titer of $1:8$, this value was selected as the definition of seroconversion.

The secondary efficacy endpoints to support evaluation of the efficacy of the ADV-7 vaccine were:

- ADV-7 febrile ARD case: a subject with one or more clinical signs and symptoms of ARD and an oral temperature $\geq 100.5^{\circ}\text{F}$ and throat culture positive for wild ADV Type-7 infection.
- ADV-7 ARD case regardless of whether the subject was febrile or not: a subject with one or more clinical signs and symptoms of ARD and throat culture positive for wild ADV-7 infection and who was too ill to perform normal training duties.
- ADV-7 booster effect: defined as the development of ADV-7 neutralizing antibody at Week 4 (Day 26) that represented at least a fourfold increase in titer from baseline (Visit 0) in a subject whose baseline ADV-7 titer was $\geq 1:4$.

Seroconversion rates observed at Week 4 (Day 26) for the ADV-4 vaccine and placebo groups were calculated and the 95% confidence intervals were obtained based on the normal approximation for the confidence interval for a proportion. Seroconversion rates at other time points, i.e., at Week 2 (Day 12) and Week 8 (Day 56) were assessed.

For the ADV-4 vaccine, vaccine efficacy in reducing the attack rate of ADV-4-associated ARD cases regardless of whether the subject was febrile or not was analyzed in the same way as those with the febrile cases (see analysis for the primary efficacy endpoint).

The booster effect for the ADV-4 and ADV-7 vaccines was analyzed in the same way as for the seroconversion rate. A combined analysis, including seroconversion and booster effect, was also done in addition to the separate analysis for the ADV-4 and ADV-7 vaccines.

8.1.1.5.3 Safety Endpoints

8.1.1.5.3.1 Adverse Events

Definitions:

Adverse Events

An adverse event (AE) was defined as any untoward reaction, side effect, or other undesirable event that occurs in conjunction with the use of a drug, biological product or diagnostic agent in humans, including intercurrent illnesses and injuries and exacerbations of preexisting conditions. AEs and concomitant diseases were coded using the Medical Dictionary for Medical Activities (MedDRA) coding dictionary. Classification of AEs can be found in Table 7.

Table 7: Classification of Adverse Events⁺

Severity	Description
Mild	Awareness of signs or symptoms; easily tolerated
Moderate	Enough discomfort to cause interference with usual activity
Severe	Incapacitating, with inability to do work or do usual activity
Life-threatening	Subject was at risk at time of the event (not an event that might have caused death if more severe)

⁺Adapted from BLA Section 5.3.5.1, page 380

Serious Adverse Events

A serious adverse event (SAE) is one that meets the following criteria:

- Fatal or life-threatening
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly
- Deemed to be an important medical event by the principal investigator or by a designated, qualified sub-investigator

The applicant notes that recruits with febrile ARD and minor injuries or illnesses often are restricted, as a matter of routine, to a self-care ward at Fort Jackson or to Sick in Quarters (SIQ) at Great Lakes. This does not reflect the severity of the illness, but rather the policy that recruits are not permitted to remain in the barracks during the training day. Therefore, admission to the self-care ward at Fort Jackson or to SIQ at Great Lakes does not necessarily denote occurrence of an SAE. All hospital admissions, however, were recorded as SAEs.

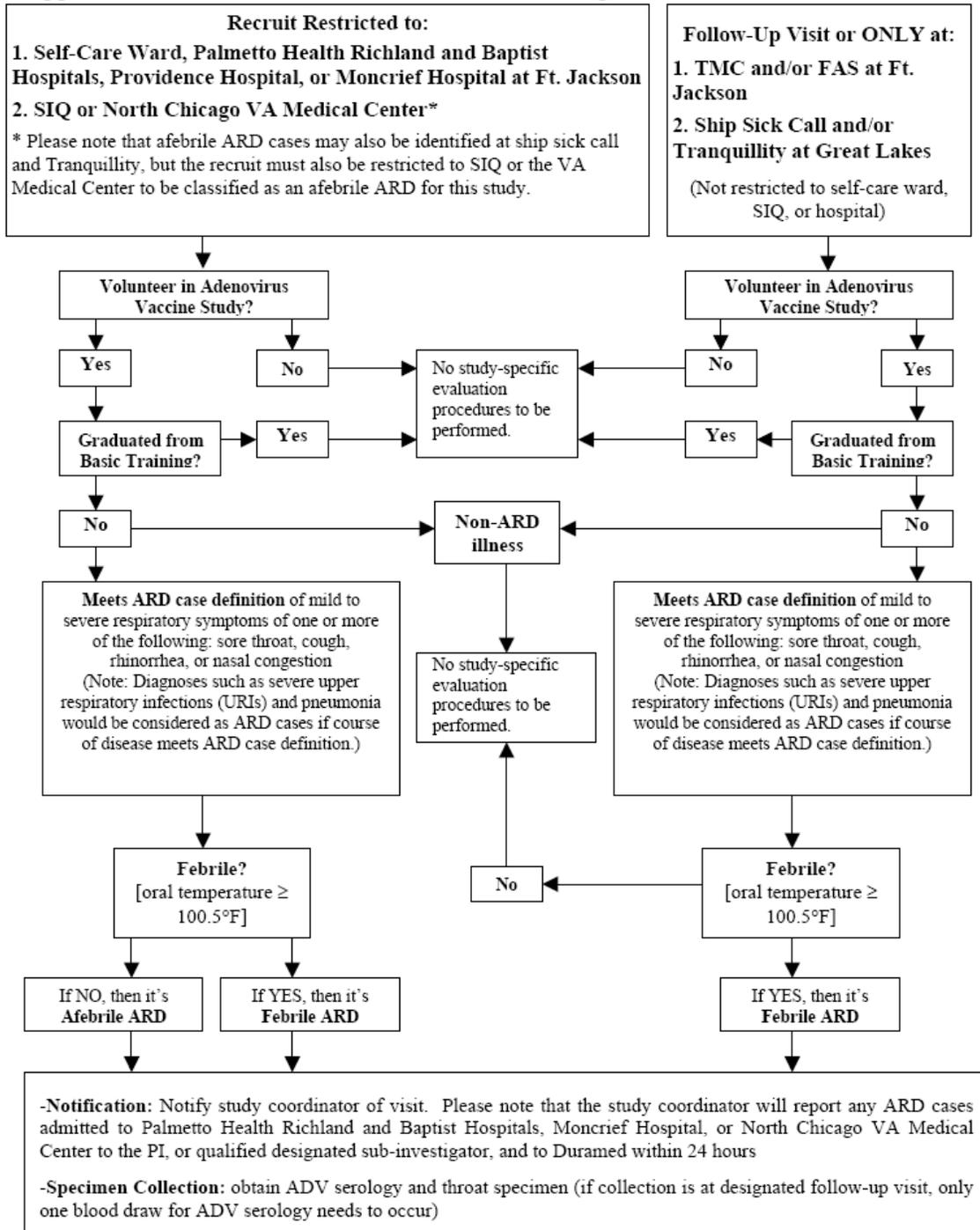
8.1.1.6 Safety Surveillance/Monitoring

- Subjects recorded post-vaccination symptoms on a 2-Week Daily Diary (for the first 780 subjects) or a 1-Week Daily Diary (for all subjects after the initial safety cohort). For each diary-based symptom, the proportion of the subjects who reported to experience the problem was presented for each treatment group over time. Severity of the symptoms (mild, moderate, severe) also was summarized.

- An independent Data Monitoring Committee (DMC) composed of a biostatistician and four clinicians, monitored the study, reviewing all blinded AEs and SAEs on a monthly basis, and conducted an interim safety assessment when the initial 780 subjects had completed the final study visit (Day 56). The DMC also performed an unblinded efficacy evaluation of the vaccine and placebo ADV-4-associated febrile ARD attack rates after 2000 subjects completed Visit 4 (Week 8) to permit an assessment of the statistical adequacy of the planned sample size of 4000 total treated subjects (3000 on vaccine, 1000 on placebo).
- Case report forms were used during the three scheduled follow-up visits (weeks 2, 4 and 8 after study medication administration) to record AEs and concomitant medications.
- Active surveillance consisted of AE and concomitant medication assessment at each of the three scheduled follow-up visits, and a determination of oral temperature. Additionally, an attempted telephone, e-mail or letter contact with each subject at 6 months after study medication administration was made to assess for SAEs and concomitant medication administration. SAE surveillance for this study included active surveillance of hospital admissions at Fort Jackson (Moncrief Hospital, Palmetto Health Richland and Baptist Hospitals, Providence Hospital) and Great Lakes (North Chicago VA, Medical Center). Passive surveillance consisted of a 1-week diary of AEs kept by recipients of study medication; members of the safety cohort (n=780) kept 2-week diaries.
- All SAEs were followed through resolution or until the PI, or designated qualified sub-investigator, assessed the SAE as chronic or stable. An attempt was made to follow-up on all SAEs to at least 30 days from the day of the event.
- During any of the three scheduled follow-up visits, if the subject reported respiratory symptoms or feeling feverish, an oral temperature was recorded. If the subject was found to have an oral temperature of $\geq 100.5^{\circ}\text{F}$ during any of the three scheduled follow-up visits, duplicate throat swabs for viral isolation were taken and an assessment of ARD cases was initiated.
- An algorithm for assessing ARD cases was provided and is reproduced below.

Figure 1: Acute Respiratory Disease Evaluation Algorithm[†]

Appendix 3 – ARD Surveillance and Evaluation Algorithm



SIQ – Sick in Quarters ; ARD – Acute Respiratory Disease; TMC – Troop Medical Clinic; FAS – Forward AID Station. Note that this study had been performed by Duramed, which subsequently was obtained by Teva Pharmaceuticals.

[†]Reproduced from BLA Section 5.3.5.1, page 407

8.1.1.7 Statistical Considerations

8.1.1.7.1 Sample Size/Statistical Power

Sample Size Required for Safety: In a 31 October 2005 letter to the applicant, the FDA asked that the safety of the vaccines be evaluated in at least 3,000 vaccinees, requiring an enrollment of at least 4,000, given the applicant's plan for a 3:1 vaccine: placebo exposure ratio.

Sample Size Calculations for Efficacy Assessments: Historical military surveillance data showed that the attack rate due to wild ADV-4 ranged from 1% - 10% among new military recruits. Assuming an 80% vaccine efficacy, with a lower bound 95% confidence interval (CI) of no lower than 60% and a 3:1 randomization allocation ratio, a total sample size of 4,000 (3,000 for vaccine and 1,000 for placebo) was sufficient for an estimated background attack rate of 5%.

Few wild ADV-7 cases were expected to be observed in the placebo group and thus it was not feasible to obtain a reasonable sample size estimate for formal analysis of the ADV-7 ARD attack rate. Therefore, the primary analysis to evaluate the efficacy of the ADV-7 vaccine was to determine the ADV-7 seroconversion rate. Assuming an expected seroconversion rate for the ADV-7 vaccine is 75% with a lower bound of a 2-sided 95% confidence interval of no less than 70%, 289 ADV-7 seronegative subjects in the vaccine group were required. According to the Phase 1 study, about 20% of the volunteers were seronegative to ADV-7 at the time of study enrollment. Since subjects would not be screened as to their ADV antibody status for enrolling in this Phase 3 study, with a 20% seronegativity rate for ADV-7 and a 90% chance of success, at least 1,606 subjects needed to be enrolled for the vaccine group in order to obtain 289 ADV-7 seronegative subjects. Adjusting for a 15% dropout rate resulted in at least 1,890 subjects for the vaccine group. The 3,000 subjects in the vaccine group were adequate for the sample size of 1,890 subjects required for the ADV-7 seroconversion evaluation.

Changes to the Statistical Analysis Plan: The following change, in agreement with FDA, was made in the seroconversion analysis before the database lock and treatment was unblinded: The immune-response data for the protocol-specified seroconversion analysis were unblinded and analyzed when an adequate number of results of serological testing had been received. Although specimens also were collected at Day 12 and Day 56, only samples obtained at Day 26 were analyzed for immunogenicity. The applicant noted in the pre-BLA clinical meeting (30 June 2008) that analyzing Day 12 and Day 56 samples would delay the submission of the BLA by at least 6 months because the laboratory that had performed the analysis on the Day 26 samples had stopped performing these tests. As a result, seroconversion and booster effect of ADV-4 and ADV-7 vaccines at Week 2 (Day 12) and Week 8 (Day 56) were not evaluated.

8.1.1.7.2 Study Cohorts Analyzed

Initial Safety Cohort: The first 780 enrollees comprised the initial safety cohort. These individuals were administered a two week diary in which to document AEs, rather than the one week diary provided to the subsequent enrollees. Members of the initial safety cohort who received vaccine (rather than placebo) were administered vaccine from Lot 1 only.

Intent to Treat Cohort: The Intent to Treat (ITT) cohort consisted of subjects enrolled subsequent to the 780 subjects enrolled in the initial safety cohort. Lots 1, 2 and 3 of the vaccine product were equally distributed among the subjects in this group who were randomized to receive vaccine. Subjects in this cohort were provided 1-week diaries to record AEs, rather than the 2-week diaries provided to subjects in the initial safety cohort.

Medical reviewer's comment: In the BLA submission, an initial table describing subject disposition (reproduced as Table 8 in this review, below) is labeled ITT/Safety Cohort. Subsequent tables which include the entire 4,040 subject population (both the ITT and Safety cohorts) are labeled "ITT Cohort." This discrepancy was addressed with the applicant and did not present difficulties in carrying out this review. In this review, tables subsequent to Table 8 which include the entire cohort similarly are labeled "ITT Cohort."

Per Protocol Cohort: The Per Protocol (PP) Cohort included all subjects who met the eligibility criteria set forth in the protocol, who did not have any significant violations or deviations from the protocol, and who completed the final study visit (Visit 4, Day 56). Subjects who vomited within 24 hours after taking the study medication were excluded from the PP cohort. This cohort was assessed in the same manner as the ITT cohort.

All Treated Cohort: For purposes of efficacy and final safety analysis, results from persons in the initial safety cohort were combined with those from the ITT cohort in the all treated cohort.

Type-4 ADV Seroconversion Cohort: Included those subjects who had a negative Type-4 ADV serum neutralizing antibody status (<1:4) at baseline and at least one titer value for ADV-4 at the subsequent visits following vaccination. This cohort was used to evaluate the seroconversion rates for the oral Type-4 vaccine group and the placebo group.

Type-7 ADV Seroconversion Cohort: Included those subjects who had a negative Type-7 ADV serum neutralizing antibody status (<1:4) at baseline and at least one titer value for ADV-7 at the subsequent visits following vaccination. This cohort was used to evaluate the seroconversion rates for the oral Type-7 vaccine group and the placebo group.

Type-4 ADV Booster Cohort: Included those subjects who had a positive Type-4 ADV serum neutralizing antibody status at baseline ($\geq 1:4$) and at least one titer value for ADV Type-4 at the subsequent visits following study medication administration. This cohort was used to evaluate the booster rates for the oral Type-4 vaccine group and the placebo group.

Type-7 ADV Booster Cohort: Included those subjects who had a positive Type-7 ADV serum neutralizing antibody status at baseline ($\geq 1:4$) and at least one titer value for ADV Type-7 at the subsequent visits following study medication administration. This cohort was used to evaluate the booster rates for the oral Type-7 vaccine group and the placebo group.

Type-4 ADV Seroconversion Booster Combined Cohort: Included those subjects who had a non-missing baseline Type-4 ADV serum neutralizing antibody and at least one titer value for ADV Type-4 at the subsequent visits following study medication administration. This cohort was used to evaluate the combined seroconversion-booster rates for the oral Type-4 vaccine group and the placebo group.

Type-7 ADV Seroconversion Booster Combined Cohort: Included those subjects who had a non-missing baseline Type-7 ADV serum neutralizing antibody and at least one titer value for ADV Type-7 at the subsequent visits following study medication administration. This cohort was used to evaluate the combined seroconversion-booster rates for the oral Type-7 vaccine group and the placebo group.

Lot-to-Lot Consistency Analysis Cohort: Included those subjects who were enrolled after the initial safety cohort of 780 subjects and randomly assigned to receive one of three lots of the vaccines.

Supplementary Lot-to-Lot Consistency Analysis Cohort: Included all subjects who were randomly assigned to receive the vaccines.

8.1.2 Results

8.1.2.1 Populations Enrolled/Analyzed

8.1.2.1.1 Study Sites and Study Period

Two study centers enrolled a total of 4041 subjects. A total of 2,010 subjects were enrolled at the Fort Jackson Military Training Post, Fort Jackson, SC, while 2,031 subjects were enrolled at the Great Lakes Naval Recruit Training Command, Great Lakes, IL.

The first subject was enrolled in the study on 30 September 2006. The last active phase study visit occurred on 02 December 2007. The last safety follow-up contact occurred in April 2008.

8.1.2.1.2 Subject Disposition and Follow-up

The number of subjects vaccinated, completed, withdrawn, and the reason for discontinuation is presented in Table 8.

Table 8: Subject Disposition: ITT/Safety Cohort[†]

Disposition	Vaccine	Placebo	Total
All Treated (ITT/Safety)	3031	1009	4040
Completed Study	2887 (95%)	955 (95%)	3842 (95%)
Did Not Complete Study	144 (5%)	54 (5%)	198 (5%)
Reason for Discontinuation - Did not meet protocol requirements	3	3	6
Reason for Discontinuation - Non-compliance with the protocol	2	2	4
Reason for Discontinuation - Investigator discretion	1	0	1
Reason for Discontinuation - Subject request to be withdrawn	17	6	23
Reason for Discontinuation - Adverse event	0	0	0
Reason for Discontinuation - Subject pregnant	2	0	2
Reason for Discontinuation - Lost to follow-up	19	8	27
Reason for Discontinuation - Other	100	35	135

[†]Reproduced from Table 6, BLA Section 5.3.5.1, page 41

One subject was randomized and excluded from the ITT cohort because of being unable to swallow the vaccine tablets after multiple attempts.

The numbers of subjects for all the analysis cohorts are summarized in Table 9. A total of 42 study completers were excluded from the PP cohort, 41 completers who vomited within the 24-hour period following the vaccine administration at Visit 1 and one who took corticosteroids within 7 days post vaccine administration.

Table 9: Analysis Cohort[†]

Analysis Subset	ADV Vaccine (N = 3032)	Placebo (N = 1009)	Total (N = 4041)
Intent-to-treat	3031	1009	4040
Per Protocol	2855	945	3800
Type-4 ADV Seroconversion Booster Combined	2935	979	3914
Type-7 ADV Seroconversion Booster Combined	2935	979	3914
Type-4 ADV Seroconversion	1841	653	2494
Type-7 ADV Seroconversion	1120	359	1479
Type-4 ADV Booster	1094	326	1420
Type-7 ADV Booster	1815	620	2435
Lot-to-Lot Consistency Analysis Cohort	2371	NA	2371
Supplementary Lot-to-Lot Consistency Analysis Cohort	3031	NA	3031

[†]Reproduced from Table 7, BLA Section 5.3.5.1, page 47

8.1.2.1.3 Subject Demographics

The demographic characteristics of the ITT cohort are summarized in Table 10. The vaccine and placebo recipient groups were comparable in demographic and baseline characteristics for all parameters. The mean (SD) age was 21.2 (4.0) years, the mean (SD) ADV-4 titer was 36.3 (111.0), and the mean (SD) ADV-7 titer was 83.9 (290.4). A total of 1,488 (36.8%) subjects were female. The racial distribution of subjects was typical of the U.S. population.

Table 10: Demographic Characteristics: ITT Cohort[†]

Demographic	ADV Vaccine (N = 3031)	Placebo (N = 1009)	Total (N = 4040)
Race: African-American	554 (18.3%)	186 (18.4%)	740 (18.3%)
Race: Asian	94 (3.1%)	29 (2.9%)	123 (3.0%)
Race: Caucasian	1871 (61.7%)	642 (63.6%)	2513 (62.2%)
Race: Hispanic	326 (10.8%)	103 (10.2%)	429 (10.6%)
Race: Other	186 (6.1%)	49 (4.9%)	235 (5.8%)
Gender: Male	1910 (63.0%)	642 (63.6%)	2552 (63.2%)
Gender: Female	1121 (37.0%)	367 (36.4%)	1488 (36.8%)
Age: Mean (Std)	21.3 (4.0)	21.1 (4.1)	21.2 (4.0)
Age: Median	19.8	19.7	19.8
Age: (Min, Max)	(17.1, 42.0)	(17.1, 42.2)	(17.1, 42.2)

[†]Reproduced from Table 8, BLA Section 5.3.5.1, page 45

The baseline serostatus of the ITT cohort is presented in Table 11. A total of 2,584 (64.0%) subjects were seronegative with respect to the ADV-4 titer; 1906 (62.9%) of 3029 who received the vaccine and 678 (67.2%) of 1009 placebo recipients. A total of 1,536 (38.0%) subjects were seronegative with respect to the ADV-7 titer; 1159 (38.3%) of 3029 who received the vaccine and 377 (37.4%) of 1009 who received the vaccine.

Medical reviewer comment: This study targeted military recruits, as the indication sought by the applicant is for use in this population. Accordingly, the subjects enrolled in this study were predominantly young, with a mean age of approximately 21 years and a median age just short of 20 years. The oldest individuals enrolled in this trial were approximately 42 years old. Given the absence of important safety signals in this Phase 3 trial, I believe it is appropriate to grant an indication for use of this product in individuals up to age 50, despite the absence of data in individuals older than age 42.

Table 11: ADV-4 and ADV-7 Serostatus (Baseline): ITT Cohort[†]

Type/Titer	ADV Vaccine	Placebo	Total
Type-4 Titer Negative*	1906	678	2584
Type-4 Titer Positive**	1123	331	1454
Type-4 Titer N	3029	1009	4038
Type-4 Titer Mean (Std)	36.0 (109.6)	37.3 (115.1)	36.3 (111.0)
Type-4 Titer Median	2.0	2.0	2.0
Type-4 Titer (Min, Max)	(2.0, 2580.3)	(2.0, 1448.2)	(2.0, 2580.3)
Type-7 Titer Negative*	1159	377	1536
Type-7 Titer Positive**	1870	632	2502
Type-7 Titer N	3029	1009	4038
Type-7 Titer Mean (Std)	83.0 (313.2)	86.7 (207.5)	83.9 (290.4)
Type-7 Titer Median	10.1	10.1	10.1
Type-7 Titer (Min, Max)	2.0, 10321.3)	(2.0, 2048.0)	(2.0, 10321.3)

*Titer value <1:4 at Visit 0

**Titer value ≥1:4 at Visit 0

[†]Reproduced from Table 8, BLA Section 5.3.5.1, page 45

8.1.2.1.4 Treatment Compliance

A total of 4,041 subjects were randomized and 4,040 subjects were vaccinated. One subject (10709) was unable to swallow the vaccine tablets and was discontinued from the study.

8.1.2.2 Primary Efficacy Endpoints

8.1.2.2.1 Primary Efficacy Endpoint: Wild ADV-4 Febrile ARD Cases

Results for the primary endpoint, wild ADV-4 febrile ARD case for the ITT cohort, are summarized in Table 12. A total of 49 wild ADV-4 febrile ARD cases were observed in this study. Among placebo recipients 48 (4.76%) of 1009 developed wild ADV-4 febrile ARD. Among the vaccine group, one case (0.03%) of 3,031 developed wild ADV-4 febrile ARD. The VE estimate was 99.31% and the corresponding 95% confidence interval of VE was (96.02%, 99.88%). As the VE estimate is greater than 80% and the lower bound of the 95% confidence interval for VE was greater than 60%, the oral ADV 4/7 Vaccine met the pre-determined criteria for superiority to the placebo in reducing wild ADV-4 febrile ARD cases.

Table 12: Wild ADV-4 Febrile ARD Rate (Day 0 - 56): ITT Cohort[†]

ADV Vaccine (N = 3031)	Placebo (N = 1009)	Vaccine Efficacy (95% CI)
1 (0.03%)	48 (4.76%)	99.31% (96.02%, 99.88%)

[†]Reproduced from Table 9, BLA Section 5.3.5.1, page 46

Wild ADV-4 febrile ARD cases by gender and age group (<18 years vs. >18 years) are summarized descriptively in Table 13. For male subjects, 1 (0.05%) case in the vaccine group and 35 (5.45%) in the placebo group were observed. For female subjects, none in the vaccine group and 13 (3.54%) in the placebo group were observed. The vaccine efficacy appeared to be comparable for the male subgroup and the female subgroup. The vaccine efficacy also appeared to be comparable for both age subgroups.

Table 13: Wild ADV-4 Febrile ARD Rate (Day 0 - 56) by Gender and Age Group: ITT Cohort[†]

Demographic	ADV Vaccine (N = 3031)	Placebo (N = 1009)
Male Total N	(n = 1910)	(n = 642)
Male ADV-4 Febrile ARD Case(s)	1 (0.05%)	35 (5.45%)
Female Total N	(n = 1121)	(n = 367)
Female ADV-4 Febrile ADV Case(s)	0 (0.00%)	13 (3.54%)
Age Group Less than 18	(n = 93)	(n = 45)
Age Group <18 ADV-4 Febrile ARD Case(s)	0 (0.00%)	3 (6.67%)
Age Group 18 and above	(n = 2938)	(n = 964)
Age Group >18 ADV-4 Febrile ARD Case(s)	1 (0.03%)	45 (4.67%)

[†]Reproduced from Table 27, BLA Section 5.3.5.1, page 57

Wild ADV-4 febrile ARD cases for the PP cohort is summarized in Table 14. A total of 48 wild ADV-4 febrile ARD cases were observed in the PP cohort with 47 (4.97%) occurring in the placebo group and 1 (0.04%) in the vaccine group. The VE estimate was 99.30% and the corresponding 95% confidence interval of VE was (95.96%, 99.88%). As the VE estimate was greater than 80% and the lower bound of the 95% confidence interval for VE was greater than 60%, the oral ADV 4/7 Vaccine met the pre-determined criteria for superiority to placebo in reducing wild ADV-4 febrile ARD cases in the PP cohort.

Table 14: Wild ADV-4 Febrile ARD Rate (Day 0 - 56): PP Cohort[†]

ADV Vaccine (N = 2855)	Placebo (N = 945)	Vaccine Efficacy (95% CI)
1 (0.04%)	47 (4.97%)	99.30% (95.96%, 99.88%)

[†]Reproduced from Table 10, BLA Section 5.3.5.1, page 46

The analysis results of wild ADV Type-4 febrile ARD case excluding those cases occurring within first 10 days following the study medication administration are presented in Table 15. The protective effect of the vaccine is unlikely to take place during this time period. A total of 44 such ARD cases were observed for the ITT cohort and all the 44 cases occurred in the placebo group. The VE estimate was 100%, supporting the claim that the adenovirus vaccine is efficacious in reducing wild ADV-4 febrile ARD cases.

Table 15: Wild ADV-4 Febrile ARD Rate (Day 11-56): ITT Cohort[†]

ADV Vaccine (N = 3031)	Placebo (N = 1009)	Vaccine Efficacy
0 (0.00%)	44 (4.36%)	100.00%

[†]Reproduced from Table 11, BLA Section 5.3.5.1, page 47

8.1.2.2 Primary Efficacy Endpoint: ADV Type-7 Seroconversion

ADV-7 seroconversion rate is presented in Table 16. A total of 1,051 ADV-7 conversions (93.8%) out of 1,120 evaluable subjects were observed in the vaccine group. The corresponding 95% confidence interval for the seroconversion rate was (92.4%, 95.2%). As the ADV-7 conversion rate is greater than 75% and the lower bound of the 2-sided 95% confidence interval is greater than 70%, the oral ADV 4/7 Vaccine met the pre-determined efficacy criterion with respect to ADV-7 seroconversion. Nineteen ADV-7 seroconversions (5.3%) out of 359 evaluable subjects were observed in the placebo group.

Table 16: ADV-7 Seroconversion Rate: ADV-7 Seroconversion Cohort[†]

Visit	Vaccine N	Vaccine # Conversion	Vaccine 95% CI	Placebo N	Placebo # Conversion	Placebo 95% CI
Week 4	1120	1051(93.8%)	(92.4%, 95.2%)	359	19 (5.3%)	(3.0%, 7.6%)

[†]Reproduced from Table 12, BLA Section 5.3.5.1, page 48

8.1.2.3 Selected Secondary Endpoint Analyses

8.1.2.3.1 Secondary Endpoint: ADV-4 Seroconversion

The ADV-4 seroconversion rate is summarized in Table 17. A total of 1,739 ADV-4 seroconversions (94.5%) out of 1,841 evaluable subjects were observed in the vaccine group. The corresponding 95% confidence interval for the seroconversion rate was (93.4%, 95.5%), which surpassed the pre-defined lower confidence limit for efficacy.

Table 17: ADV-4 Seroconversion Rate: ADV-4 Seroconversion Cohort[†]

Visit	Vaccine N	Vaccine # Conversion	Vaccine 95% CI	Placebo N	Placebo # Conversion	Placebo 95% CI
Week 4	1841	1739(94.5%)	(93.4%, 95.5%)	653	69(10.6%)	(8.2%, 12.9%)

[†]Reproduced from Table 13, BLA Section 5.3.5.1, page 48

8.1.2.3.2 Secondary Endpoint: ADV-4 ARD Case (Febrile and Afebrile)

A total of 68 wild ADV-4 ARD cases were observed in this study with 65 (6.44%) in the placebo group and 3 (0.10%) in the vaccine group (Table 18). The VE estimate was 98.46% and the corresponding 95% confidence interval of VE was (95.39%, 99.49%). The VE estimate and the 95% confidence interval exceeded the criteria of a VE of at least 80% and the lower bound of 95% confidence interval of at least 60% for the primary endpoint: wild ADV-4 febrile ARD case.

Table 18: Wild ADV-4 ARD Rate Including Both Febrile and Afebrile (Day 0-56): ITT Cohort[†]

ADV Vaccine (N = 3031)	Placebo (N = 1009)	Vaccine Efficacy
3 (0.10%)	65 (6.44%)	98.46% (95.39%, 99.49%)

[†]Reproduced from Table 14, BLA Section 5.3.5.1, page 49

8.1.2.3.3 Secondary Endpoint: ADV-4 Booster Effect

An additional secondary endpoint related to immunogenicity for the ADV-4 component was the booster rate—the proportion of those who entered the study with existing neutralizing antibodies to ADV-4 (ADV-4 neutralizing antibody titers $\geq 1:4$) and who received vaccine increased their ADV-4 neutralizing titer by fourfold or greater as compared to placebo recipients. The ADV-4 booster rate is presented in Table 19. A total of 550 ADV-4 boosters (50.3%) out of 1,094 evaluable subjects were observed in the vaccine group compared with 2 (0.6%) out of 326 evaluable subjects observed in the placebo group.

Table 19: ADV-4 Booster Rate: ADV-4 Booster Cohort ⁺

Visit	Vaccine N	Vaccine # Boosted	Vaccine 95% CI	Placebo N	Placebo # Boosted	Placebo 95% CI
Week 4	1094	550(50.3%)	(47.3%, 53.2%)	326	2(0.6%)	(-0.2%, 1.5%)

⁺Adapted from Table 15, BLA Section 5.3.5.1, page 49

*Boosted defined as a ≥ 4 -fold rise in ADV-4 neutralizing antibody titer

8.1.2.3.4 Secondary Endpoint – ADV-4 Combined Seroconversion-Booster Rate

ADV-4 combined seroconversion-booster rate is shown in Table 20. A total of 2,289 ADV-4 conversions/boosters (78.0%) out of 2,935 evaluable subjects were observed in the vaccine group compared with 71 (7.3%) out of 979 evaluable subjects in the placebo group.

Table 20: ADV-4 Combined Seroconversion-Booster Rate: ADV-4 Seroconversion-Booster Combined Cohort ⁺

Visit	Vaccine N	Vaccine # Conversion	Vaccine 95% CI	Placebo N	Placebo # Conversion	Placebo 95% CI
Week 4	2935	2289(78.0%)	(76.5%, 79.5%)	979	71(7.3%)	(5.6%, 8.9%)

⁺Reproduced from Table 16, BLA Section 5.3.5.1, page 49

8.1.2.3.5 Secondary Endpoint – ADV-7 ARD Case (Febrile and Afebrile)

No ADV-7 febrile and/or afebrile ARD case was observed in this study.

8.1.2.3.6 Secondary Endpoint – ADV-7 Booster Effect

ADV-7 booster rate is presented in Table 21. A total of 836 ADV-7 boosters (46.1%) out of 1,815 evaluable subjects were observed in the vaccine group compared with 24 (3.9%) out of 620 evaluable subjects observed in the placebo group.

Table 21: ADV-7 Booster Rate: ADV-7 Booster Cohort⁺

Visit	Vaccine N	Vaccine # Conversion	Vaccine 95% CI	Placebo N	Placebo # Conversion	Placebo 95% CI
Week 4	1815	836(46.1%)	(43.8%, 48.4%)	620	24(3.9%)	(2.4%, 5.4%)

⁺Reproduced from Table 17, BLA Section 5.3.5.1, page 50

*Boosted defined as a ≥ 4 -fold rise in ADV-4 neutralizing antibody titer

8.1.2.3.7 Secondary Endpoint – ADV-7 Combined Seroconversion-Booster Rate

ADV Type-7 combined seroconversion-booster rate is presented in Table 22. A total of 1,887 ADV-7 conversions/boosters (64.3%) out of 2,935 evaluable subjects were observed in the vaccine group compared with 43 (4.4%) out of 979 evaluable subjects in the placebo group. As was the case for the ADV-4 combined seroconversion-booster rate, the treatment difference in ADV-7 combined seroconversion-booster rate favored the vaccine.

Table 22: ADV-7 Combined Seroconversion-Booster Rate: ADV-7 Seroconversion-Booster Combined Cohort⁺

Visit	Vaccine N	Vaccine # Conversion	Vaccine 95% CI	Placebo N	Placebo # Conversion	Placebo 95% CI
Week 4	1815	836(46.1%)	(43.8%, 48.4%)	620	24(3.9%)	(2.4%, 5.4%)

⁺Reproduced from Table 18, BLA Section 5.3.5.1, page 50

8.1.2.4 Consistency of Manufacturing Lots

Lot-to-lot consistency analysis was performed for the following two cohorts: 1) lot-to-lot consistency cohort; and 2) supplementary lot-to-lot consistency analysis cohort. The objective was to demonstrate the consistency of three consecutively manufactured vaccine lots of ADV-4 and ADV-7 through the evaluation of the immunogenicity response in study participants. Three vaccine lots of both ADV-4 and ADV-7 vaccine tablets were used to provide data for the analysis of lot-to-lot consistency. Each ADV-4 vaccine lot was paired with a single ADV-7 vaccine lot only. (For example, Lot 1 of ADV-4 was paired with Lot 1 of ADV-7, Lot 2 of ADV-4 was paired with Lot 2 of ADV-7, and Lot 3 of ADV-4 was paired with Lot 3 of ADV-7.

The lot-to-lot consistency analysis was performed on approximately 2,415 subjects who were enrolled after the initial safety cohort of 780 subjects, and randomly assigned to receive one of three lots of the vaccines. Lots were determined to be consistent if the two-sided 95% CIs for pairwise post-study medication administration (Week 4, Day 26 \pm 4 days) GMT ratios of antibody titers were within the boundaries of (0.5, 2.0). A supplementary analysis of lot-to-lot consistency also was performed that included all subjects treated with vaccine, i.e., both subjects treated with vaccine in the initial safety cohort and subjects treated with vaccine thereafter.

The antibody titer data were transformed into the scale of natural logarithm first. The natural log transformed data were analyzed using ANOVA (or ANCOVA with the baseline data as a covariate) model. The two-sided 95% CI for pairwise mean differences in the scale of natural logarithm were transformed back to the CIs in the original scale for the corresponding GMT ratios. All the antibody data were used in the analysis of lot-to-lot consistency and missing data were not imputed.

Lot-to-lot consistency analysis cohort for ADV-4 titer: Descriptive statistics and LS means from the ANOVA model for the natural logarithm transformed ADV-4 titer for the three vaccine lots are presented in Table 23. Pair-wise GMT ratios for the three vaccine lots and the corresponding 95% confidence intervals (CI) for the GMT ratios are summarized in Table 24.

The 95% CI for the GMT ratios Lot 1/Lot 2, Lot 2/Lot 3, and Lot 1/Lot 3 were (0.79, 1.05), (0.82, 1.09), and (0.75, 0.99) respectively and all were within the boundaries of (0.50, 2.00). It was concluded that the three vaccine lots are consistent with respect to ADV-4 titer.

Table 23A & 23B: Mean Natural Logarithm Transformed ADV-4 Titer (Day 26): Lot-to-Lot Consistency Analysis Cohort [†]

Statistical Measure	Lot 1	Lot 2	Lot 3
N	759	763	763
Mean	4.46	4.56	4.61
LS Mean*	4.46	4.56	4.61
SD	1.49	1.41	1.37
Min - Max	(0.69 – 8.20)	(0.69 – 9.59)	(0.69 – 9.36)

Statistical Measure	Lot 1 – Lot 2	Lot 2 – Lot 3	Lot 1 – Lot 3
LS Mean Difference*	-0.09	-0.06	-0.15
95% CI for LS Mean Difference	(-0.24, 0.05)	(-0.20, 0.09)	(-0.29, -0.01)

* From the analysis of variance model, $\log(\text{titer}) = \text{Lot}$

[†]Reproduced from Table 19, BLA Section 5.3.5.1, page 51

Table 24: ADV-4 Geometric Mean Titer Ratio (Day 26): Lot-to-Lot Consistency Analysis Cohort [†]

Statistical Measure	Lot 1/Lot 2	Lot 2/Lot 3	Lot 1/Lot 3
GMT Ratio	0.91	0.95	0.86
95% CI for GMT Ratio	(0.79, 1.05)	(0.82, 1.09)	(0.75, 0.99)

[†]Reproduced from Table 20, BLA Section 5.3.5.1, page 51

Lot-to-lot consistency analysis cohort for ADV-7 titer: Descriptive statistics and LS means from the ANOVA model for the natural logarithm transformed ADV-7 titer for the 3 vaccine lots are presented in Table 25. Pair-wise GMT ratios for the three vaccine lots and the corresponding 95% confidence intervals for the GMT ratios are summarized in Table 26.

The 95% confidence intervals for the GMT ratios Lot1/Lot2, Lot2/Lot3, and Lot1/Lot3 were (0.81, 1.09), (0.77, 1.03), and (0.72, 0.97) respectively. All were within the pre-defined limits of (0.50, 2.00). It was concluded that the three vaccine lots are consistent with respect to the ADV-7 titer.

Table 25A & 25B: Mean Natural Logarithm Transformed ADV-7 Titer (Day 26): Lot-to-Lot Consistency Analysis Cohort [†]

Statistical Measure	Lot 1	Lot 2	Lot 3
N	759	763	763
Mean	5.27	5.33	5.45
LS Mean [*]	5.27	5.33	5.45
SD	1.52	1.49	1.36
Min - Max	(0.69 – 9.59)	(0.69 – 9.13)	(0.69 – 9.24)

Statistical Measure	Lot 1 – Lot 2	Lot 2 – Lot 3	Lot 1 – Lot 3
LS Mean Difference [*]	-0.06	-0.12	-0.18
95% CI for LS Mean Difference	(-0.21, 0.09)	(-0.27, 0.03)	(-0.33, -0.03)

^{*}From the analysis of variance model, $\log(\text{titer}) = \text{Lot}$

[†]Reproduced from Table 21, BLA Section 5.3.5.1, page 52

Table 26: ADV-7 Geometric Mean Titer Ratio (Day 26): Lot-to-Lot Consistency Analysis Cohort [†]

Statistical Measure	Lot 1/Lot 2	Lot 2/Lot 3	Lot 1/Lot 3
GMT Ratio	0.94	0.89	0.83
95% CI for GMT Ratio	(0.81, 1.09)	(0.77, 1.03)	(0.72, 0.97)

[†]Reproduced from Table 20, BLA Section 5.3.5.1, page 51

Medical reviewer’s comment: *As lot consistency was established for the three lots used in the definitive Phase 3 study, data from all three lots were pooled for the primary evaluation of safety, immunogenicity and efficacy.*

Supplementary lot-to-lot consistency analysis cohort for ADV-4 titer: Descriptive statistics and LS means from the ANOVA model for the natural logarithm transformed ADV-4 titer for the three vaccine lots are presented in Table 27. Pair-wise GMT ratios for the three vaccine lots and the corresponding 95% CIs for the GMT ratios are summarized in Table 28.

The 95% CI for the GMT ratios Lot 1/Lot 2, Lot 2/Lot 3 and Lot 1/Lot 3 were (0.88, 1.13), (0.82, 1.09), and (0.83, 1.07) respectively and all were within the boundaries of (0.50, 2.00), supporting the previous conclusion that the three vaccine lots are consistent with respect to ADV-4 titer.

Table 27A & 27B: Mean Natural Logarithm Transformed ADV-4 Titer (Day 26): Supplementary Lot-to-Lot Consistency Analysis Cohort ⁺

Statistical Measure	Lot 1	Lot 2	Lot 3
N	1410	763	763
Mean	4.55	4.56	4.61
LS Mean*	4.55	4.56	4.61
SD	1.52	1.41	1.37
Min - Max	(0.69 – 8.66)	(0.69 – 9.59)	(0.69 – 9.36)

Statistical Measure	Lot 1 – Lot 2	Lot 2 – Lot 3	Lot 1 – Lot 3
LS Mean Difference*	-0.00	-0.06	-0.15
95% CI for LS Mean Difference	(-0.13, 0.13)	(-0.20, 0.09)	(-0.29, -0.01)

*From the analysis of variance model, $\log(\text{titer}) = \text{Lot}$

⁺Reproduced from Table 23, BLA Section 5.3.5.1, page 53

Table 28: ADV-4 Geometric Mean Titer Ratio (Day 26): Supplementary Lot-to-Lot Consistency Analysis Cohort ⁺

Statistical Measure	Lot 1/Lot 2	Lot 2/Lot 3	Lot 1/Lot 3
GMT Ratio	1.00	0.95	0.86
95% CI for GMT Ratio	(0.88, 1.13)	(0.82, 1.09)	(0.75, 0.99)

⁺Reproduced from Table 24, BLA Section 5.3.5.1, page 53

Supplementary lot-to-lot consistency analysis cohort for ADV-7 titer: Descriptive statistics and LS means from the ANOVA model for the natural logarithm transformed ADV-7 titer for the three vaccine lots are presented in Table 29. Pair-wise GMT ratios for the three vaccine lots and the corresponding 95% CIs for the GMT ratios are summarized in Table 30.

The 95% CI for the GMT ratios Lot 1/Lot 2, Lot 2/Lot 3 and Lot 1/Lot 3 were (0.88, 1.14), (0.77, 1.03), and (0.78, 1.01) respectively and all were within the boundaries of (0.50, 2.00), supporting the previous conclusion that the three vaccine lots are consistent with respect to ADV-7 titer.

Table 29A & 29B: Mean Natural Logarithm Transformed ADV-7 Titer (Day 26): Supplementary Lot-to-Lot Consistency Analysis Cohort ⁺

Statistical Measure	Lot 1	Lot 2	Lot 3
N	1410	763	763
Mean	5.33	5.33	5.45
LS Mean*	5.33	5.33	5.45
SD	1.53	1.49	1.36
Min - Max	(0.69 – 11.09)	(0.69 – 9.13)	(0.69 – 9.24)

Statistical Measure	Lot 1 – Lot 2	Lot 2 – Lot 3	Lot 1 – Lot 3
LS Mean Difference*	-0.00	-0.12	-0.12
95% CI for LS Mean Difference	(-0.13, 0.13)	(-0.27, 0.03)	(-0.25, 0.01)

⁺Reproduced from Table 25, BLA Section 5.3.5.1, pages 53-54

Table 30: ADV-7 Geometric Mean Titer Ratio (Day 26): Supplementary Lot-to-Lot Consistency Analysis Cohort[†]

Statistical Measure	Lot 1/Lot 2	Lot 2/Lot 3	Lot 1/Lot 3
GMT Ratio	1.00	0.89	0.89
95% CI for GMT Ratio	(0.88, 1.14)	(0.77, 1.03)	(0.78, 1.01)

[†]Reproduced from Table 26, BLA Section 5.3.5.1, page 54

8.1.2.5 Safety Outcomes

8.1.2.5.1 Adverse Events

An overview of adverse events (AEs) is presented in Table 31. A total of 3,733 (92.40%) subjects reported 17,654 treatment-emergent AEs, and 47 (1.16%) subjects reported 57 serious adverse events (SAEs). No subject discontinued the study due to AEs, and no deaths were reported in the study. The incidences of AEs and SAEs are similar for the two treatment groups.

Table 31: Overview of Adverse Events: ITT Cohort[†]

Adverse Event Type	Vaccine (N = 3031)	Vaccine %	Placebo (N = 1009)	Placebo %
Subjects with Any Treatment-emergent AEs	2786	91.92	947	93.86
No. of Treatment-emergent AEs	13128		4526	
Subjects with any SAEs	35	1.15	12	1.19
Number of SAEs	42		15	
Subjects Discontinued due to AEs	0		0	
Deaths	0		0	

[†]Reproduced from Table 28, BLA Section 5.3.5.1, page 59

Treatment-emergent AEs were the events that occurred on or after the vaccination date (Day 0) until the final study visit (Day 56). Treatment-related AEs were the treatment-emergent events possibly, likely, or definitely related to the study medication, as judged by investigational site personnel.

Treatment-emergent AEs were further subdivided into solicited and unsolicited AEs. The term “solicited” AEs corresponds to those AEs that were recorded in prescribed fields in diaries provided to the subjects for use over a 2-week period (for the initial 780 subjects – the Safety Cohort) or for one week (for the remaining 3260 subjects). Additionally, any AE reported by a subject up to and including the Day 14 study visit was recorded as “solicited.” “Non-solicited” AEs were those AEs reported at any other time during the study, including regularly scheduled follow-up visits from Visit 3 onwards.

Medical reviewer comment: Based on the definitions provided above, all solicited adverse events occurred within the first two weeks following administration of the vaccine.

When comparing these approaches to presenting AE incidence, the combined total across solicited and non-solicited subsets may be slightly greater than the overall incidence rates that appear in Tables 32 and 33, below. This is because the non-solicited rates, as calculated, are independent of whether a subject may have reported that same AE as solicited. Accordingly, a particular AE that may have been reported in the diary and also separately reported at the scheduled visit would be counted in both the solicited and the non-solicited AE incidence rate tables.

Medical reviewer comment: This approach to reporting solicited and non-solicited AEs, while not traditional, would tend to overstate the incidence of AEs occurring within the first 14 days of the study by potentially counting an AE both as solicited and non-solicited.

The most common (1% or more) solicited and non-solicited, treatment-emergent AEs are summarized by body system in descending order in Table 32 and Table 33 respectively. The most common solicited, treatment-emergent AEs were Headache (33.4% among vaccine recipients, 34.6% among placebo recipients), Nasal Congestion (17.9%, 16%), Pharyngolaryngeal Pain (16.4%, 15.6%), Cough (15%, 15.6%), Nausea (15.4%, 15.8%). The most common non-solicited, treatment-emergent AEs were Upper Respiratory Tract Infection (39.4% among vaccine recipients, 42.0% among placebo recipients), Arthralgia (24.9%; 25.5%), Abdominal Pain Upper (15.7%, 17.1%), Procedural Pain (15.6%, 13.0%), and Headache (13.0%, 17.5%).

Medical reviewer's comment: The incidences for the preferred terms for both solicited and non-solicited, treatment-emergent AEs were comparable for vaccine and placebo recipients. The reported AEs largely seemed to reflect the broad nature of physical complaints that might be expected to be reported by individuals undergoing basic military training, as was the case for the individuals enrolled in this Phase 3 study. Of note, the incidence of pyrexia, chills and fatigue were low overall, and no higher in the vaccinees than in the placebo recipients. As these general symptoms might be expected if the administration of these live, non-attenuated viral vaccines were to result in viremia, the apparent lack of an increase in these symptoms in vaccinees vis a vis placebo recipients reduces the concern about the potential for the occurrence of viremia following vaccine administration. It must be noted, however, that subjects in this study were not able to monitor their own body temperatures in the days following vaccine administration, given the rigors and limitations of military boot camp. Reports of pyrexia were made following a subject's presentation to the camp clinic and were defined as an oral temperature of ≥ 100.5 °F.

Table 32: Incidence of Treatment-Emergent, Solicited Adverse Events: ITT Cohort (1% or more)[†]

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
ANY AE - TOTAL	1685	55.59	563	55.80	2248	55.64
NERVOUS SYSTEM DISORDERS - HEADACHE	1013	33.42	349	34.59	1362	33.71
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - TOTAL	922	30.42	300	29.73	1222	30.25
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS NASAL - CONGESTION	542	17.88	161	15.96	703	17.40
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - PHARYNGOLARYNGEAL PAIN	496	16.36	157	15.56	653	16.16
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - COUGH	452	14.91	157	15.56	609	15.07
GASTROINTESTINAL DISORDERS -TOTAL	677	22.34	212	21.01	889	22.00
GASTROINTESTINAL DISORDERS - NAUSEA	466	15.37	159	15.76	625	15.47
GASTROINTESTINAL DISORDERS - DIARRHOEA	344	11.35	99	9.81	443	10.97
GASTROINTESTINAL DISORDERS - ABDOMINAL PAIN UPPER	5	0.16	4	0.40	9	0.22
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - ARTHRALGIA	37	1.22	14	1.39	51	1.26

[†]From Table 2, BLA Information Amendment, 16 December 2010, Module 1.11.4, page 9

Table 33: Incident of Treatment-Emergent, Non-Solicited Adverse Events: ITT Cohort (1% or more)[†]

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
INFECTIONS AND INFESTATIONS - UPPER RESPIRATORY TRACT INFECTION	1193	39.36	424	42.02	1617	40.02
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - ARTHRALGIA	755	24.91	257	25.47	1012	25.05
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - PAIN IN EXTREMITY	233	7.69	72	7.14	305	7.55
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - BACK PAIN	110	3.63	56	5.55	166	4.11
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - SHOULDER PAIN	78	2.57	29	2.87	107	2.65
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - MYALGIA	54	1.78	26	2.58	80	1.98
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - MUSCULOSKELETAL CHEST PAIN	43	1.42	12	1.19	55	1.36

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - PERIOSTITIS	31	1.02	8	0.79	39	0.97
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - PHARYNGOLARYNGEAL PAIN	307	10.13	94	9.32	401	9.93
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - COUGH	290	9.57	100	9.91	390	9.65
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - NASAL CONGESTION	260	8.58	80	7.93	340	8.42
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - RHINORRHOEA	139	4.59	25	2.48	164	4.06
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - EPISTAXIS	69	2.28	21	2.08	90	2.23
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - RESPIRATORY TRACT CONGESTION	47	1.55	18	1.78	65	1.61
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - DYSPNOEA	45	1.48	13	1.29	58	1.44
GASTROINTESTINAL DISORDERS - ABDOMINAL PAIN UPPER	477	15.74	172	17.05	649	16.06
GASTROINTESTINAL DISORDERS - VOMITING	181	5.97	68	6.74	249	6.16
GASTROINTESTINAL DISORDERS - NAUSEA	121	3.99	48	4.76	169	4.18
GASTROINTESTINAL DISORDERS - DIARRHOEA	65	2.14	19	1.88	84	2.08
GASTROINTESTINAL DISORDERS - TOOTHACHE	65	2.14	14	1.39	79	1.96
GASTROINTESTINAL DISORDERS - CONSTIPATION	36	1.19	13	1.29	49	1.21
GASTROINTESTINAL DISORDERS - ABDOMINAL PAIN	35	1.15	11	1.09	46	1.14
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - PROCEDURAL PAIN	475	15.67	131	12.98	606	15.00
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - JOINT SPRAIN	65	2.14	20	1.98	85	2.10
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - ARTHROPOD BITE	22	0.73	16	1.59	38	0.94
NERVOUS SYSTEM DISORDERS - HEADACHE	399	13.16	177	17.54	576	14.26
NERVOUS SYSTEM DISORDERS - DIZZINESS	124	4.09	49	4.86	173	4.28
NERVOUS SYSTEM DISORDERS - SYNCOPE	32	1.06	8	0.79	40	0.99
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - PYREXIA	139	4.59	60	5.95	199	4.93

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - PAIN	92	3.04	43	4.26	135	3.34
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - CHILLS	84	2.77	55	5.45	139	3.44
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - FATIGUE	54	1.78	20	1.98	74	1.83
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OEDEMA PERIPHERAL	47	1.55	20	1.98	67	1.66
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - RASH	70	2.31	29	2.87	99	2.45
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - BLISTER	50	1.65	19	1.88	69	1.71
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - ACNE	18	0.59	3	0.30	21	0.52
EAR AND LABYRINTH DISORDERS -EAR PAIN	57	1.88	19	1.88	76	1.88
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - DYSMENORRHOEA	31	1.02	11	1.09	42	1.04
METABOLISM AND NUTRITION DISORDERS - DEHYDRATION	39	1.29	16	1.59	55	1.36
BLOOD AND LYMPHATIC SYSTEM DISORDERS - LYMPHADENOPATHY	23	0.76	16	1.59	39	0.97

From Table 1, BLA Information Amendment, 16 December 2010, Module 1.11.4, pages 7 - 8

The most common (1% or more) solicited and non-solicited, treatment-related AEs are summarized by body system in descending order in Table 34 and 35, respectively. The most common solicited, treatment-related AEs were Headache (30.75% among vaccine recipients, 31.81% among placebo recipients), Nasal Congestion (16.89%; 15.16%), Pharyngolaryngeal Pain (15.28%, 14.67%), Nausea (14.55%, 14.67%) and Cough (14.32%, 14.27%). The most common non-solicited, treatment-related AEs were Upper Respiratory Tract Infection (37.35% among vaccine recipients, 39.35% among placebo recipients), Arthralgia (17.29%, 17.84%), Abdominal Pain Upper (14.62%, 15.56%), and Headache (10.89%, 14.67%).

Pyrexia (temperature $\geq 100.5^{\circ}\text{F}$) within seven days was reported to occur in 1.4% (42/3030) of vaccine recipients and 0.5% (5/961) of placebo recipients who were not diagnosed with ARD. During the 8-14 days post-vaccination, rates of pyrexia were 0.6% (4/659) and 1.1% (2/170) in vaccine and placebo recipients, respectively.

Medical reviewer's comment: The incidences for the preferred terms for both solicited and non-solicited, treatment-related AEs were comparable for vaccine and placebo recipients. As was the case for treatment-emergent AEs, the reported AEs considered treatment-related also seemed to reflect the kinds of physical complaints that might be expected to be reported by individuals undergoing basic military training. The pyrexia data does not suggest any meaningful difference in pyrexia incidence between vaccinees and placebo recipients occurring in the first two weeks following vaccine administration.

Table 34: Incidence of Treatment-Related, Solicited Adverse Events: ITT Cohort (1% or more)⁺

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
ANY AE - Total	1605	52.95	530	52.53	2135	52.85
NERVOUS SYSTEM DISORDERS - HEADACHE	932	30.75	321	31.81	1253	31.01
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Total	864	28.51	279	27.65	1143	28.29
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - NASAL CONGESTION	512	16.89	153	15.16	665	16.46
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - PHARYNGOLARYNGEAL PAIN	463	15.28	148	14.67	611	15.12
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - COUGH	434	14.32	144	14.27	578	14.31
GASTROINTESTINAL DISORDERS - Total Disorders	646	21.31	198	19.62	844	20.89
GASTROINTESTINAL DISORDERS - NAUSEA	441	14.55	148	14.67	589	14.58
GASTROINTESTINAL DISORDERS - DIARRHOEA	328	10.82	94	9.32	422	10.45
GASTROINTESTINAL DISORDERS - ABDOMINAL PAIN UPPER	5	0.16	4	0.40	9	0.22
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - ARTHRALGIA	33	1.09	13	1.29	46	1.14

From Table 4, BLA Information Amendment, 16 December 2010, Module 1.11.4, p. 12

Table 35: Incidence of Treatment-Related, Non-Solicited Adverse Events: ITT Cohort (1% or more)⁺

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
ANY AE - Total	2364	77.99	827	81.96	3191	78.99
INFECTIONS AND INFESTATIONS - UPPER RESPIRATORY TRACT INFECTION	1135	37.45	397	39.35	1532	37.92
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - COUGH	257	8.48	91	9.02	348	8.61
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - PHARYNGOLARYNGEAL PAIN	253	8.35	73	7.23	326	8.07

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - NASAL CONGESTION	229	7.56	73	7.23	302	7.48
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - RHINORRHOEA	128	4.22	25	2.48	153	3.79
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - EPISTAXIS	45	1.48	17	1.68	62	1.53
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - RESPIRATORY TRACT CONGESTION	44	1.45	18	1.78	62	1.53
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - DYSPNOEA	42	1.39	8	0.79	50	1.24
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - ARTHRALGIA	524	17.29	180	17.84	704	17.43
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - PAIN IN EXTREMITY	130	4.29	37	3.67	167	4.13
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - BACK PAIN	84	2.77	44	4.36	128	3.17
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - SHOULDER PAIN	54	1.78	17	1.68	71	1.76
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - MYALGIA	47	1.55	24	2.38	71	1.76
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - MUSCULOSKELETAL CHEST PAIN	35	1.15	8	0.79	43	1.06
GASTROINTESTINAL DISORDERS - ABDOMINAL PAIN UPPER	443	14.62	157	15.56	600	14.85
GASTROINTESTINAL DISORDERS - VOMITING	160	5.28	55	5.45	215	5.32
GASTROINTESTINAL DISORDERS - NAUSEA	102	3.37	39	3.87	141	3.49
GASTROINTESTINAL DISORDERS - DIARRHOEA	60	1.98	18	1.78	78	1.93
GASTROINTESTINAL DISORDERS - TOOTHACHE	32	1.06	7	0.69	39	0.97
GASTROINTESTINAL DISORDERS - CONSTIPATION	29	0.96	12	1.19	41	1.01
NERVOUS SYSTEM DISORDERS - HEADACHE	330	10.89	148	14.67	478	11.83
NERVOUS SYSTEM DISORDERS - DIZZINESS	101	3.33	35	3.47	136	3.37
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -PYREXIA	126	4.16	49	4.86	175	4.33
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -PAIN	79	2.61	37	3.67	116	2.87

MedDRA System Organ Class and Preferred Term	Vaccine N=3031	Vaccine %	Placebo N=1009	Placebo %	Total N=4040	Total %
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -CHILLS	77	2.54	51	5.05	128	3.17
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -FATIGUE	49	1.62	18	1.78	67	1.66
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -OEDEMA PERIPHERAL	37	1.22	14	1.39	51	1.26
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - JOINT SPRAIN	56	1.85	17	1.68	73	1.81
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - RASH	40	1.32	17	1.68	57	1.41
SKIN AND SUBCUTANEOUS TISSUE DISORDERS -BLISTER	34	1.12	11	1.09	45	1.11
EAR AND LABYRINTH DISORDERS -EAR PAIN	52	1.72	18	1.78	70	1.73
METABOLISM AND NUTRITION DISORDERS - DEHYDRATION	37	1.22	13	1.29	50	1.24
BLOOD AND LYMPHATIC SYSTEM DISORDERS - LYMPHADENOPATHY	22	0.73	16	1.59	38	0.94

[†]From Table 3, BLA Information Amendment, 16 December 2010, Module 1.11.4, pp. 10-11

Medical reviewer’s comment: The comparable incidence of non-solicited and solicited AEs, whether classified as treatment-emergent or treatment-related, between vaccine and placebo recipients, suggests that the vaccine is safe and was well-tolerated.

8.1.2.5.2 Serious Adverse Events

There were no deaths among study subjects during the study period. All serious adverse events (SAEs) based on the locked database (17 March 2008 (section 16.5)) are listed in Table 36.

Table 36: Listing of Serious Adverse Events[†]

Treatment	Site	Subj	Serious AE (Verbatim)	AE Start	AE Stop	AE Severity	Causality	Discontinue
Vaccines	0001	10217	ADJUSTMENT DISORDER	27APR2007	Ongoing	Severe	Remotely	No
Vaccines	0001	10218	RIGHT HIP FRACTURE	23JAN2007	09MAY2007	Severe	Remotely	No
Vaccines	0001	10219	PYELONEPHRITIS	10JAN2007	12FEB2007	Severe	Remotely	No
Vaccines	0001	10251	OVERDOSE ON IBUPROFEN	17MAR2007	18MAR2007	Severe	Remotely	No
Vaccines	0001	10251	ADJUSTMENT DISORDER	17MAR2007	Ongoing	Severe	Remotely	No
Vaccines	0001	10340	CONCUSSION	04JUL2007	Ongoing	Severe	None	No
Vaccines	0001	10949	ACUTE BRONCHITIS	17JUL2007	18SEP2007	Severe	Remotely	No
Vaccines	0001	10982	ACUTE ELECTRICAL INJURY SECONDARY TO LIGHTENING STRIKE	11JUL2007	11JUL2007	Severe	None	No
Vaccines	0001	10987	BROKEN JAW	04NOV2007		Severe	None	No

Treatment	Site	Subj	Serious AE (Verbatim)	AE Start	AE Stop	AE Severity	Causality	Discontinue
Vaccines	0001	10996	HEMATURIA	31MAY2007	01JUN2007	Severe	Possibly	No
Vaccines	0001	10996	GASTROENTERITIS	31MAY2007	02JUN2007	Severe	Possibly	No
Vaccines	0001	11052	LEFT INGUINAL HERNIA	12JUL2007	24AUG2007	Severe	Remotely	No
Vaccines	0001	11052	RIGHT INGUINAL HERNIA	03OCT2007	27NOV2007	Severe	Remotely	No
Vaccines	0001	11077	PNEUMONIA	27JUN2007	15JUL2007	Severe	Possibly	No
Vaccines	0001	11099	GRAVES DISEASE	16JUL2007	Ongoing	Severe	Remotely	No
Vaccines	0001	11161	CELLULITIS RIGHT FOOT	23JUL2007	03SEP2007	Severe	Remotely	No
Vaccines	0001	11279	GASTRITIS	15AUG2007	02OCT2007	Severe	Possibly	No
Vaccines	0001	11294	LEFT LEG CELLULITIS	25AUG2007	07SEP2007	Severe	Remotely	No
Vaccines	0001	11439	FEBRILE GASTROENTERITIS	10AUG2007	19SEP2007	Severe	Possibly	No
Vaccines	0001	11444	INTENTIONAL OVERDOSE	21AUG2007	22AUG2007	Severe	Remotely	No
Vaccines	0001	11582	FRACTURED SPINE	30DEC2007		Severe	None	No
Vaccines	0001	11588	RIGHT KNEE ACL COMPLETE TEAR	03SEP2007	Ongoing	Severe	Remotely	No
Vaccines	0001	11673	DRUG OVERDOSE	28SEP2007	28SEP2007	Severe	Remotely	No
Vaccines	0001	11794	HEMATOCHEZIA	17NOV2007	30NOV2007	Severe	Possibly	No
Vaccines	0001	11844	LEFT KNEE ACL INJURY	12OCT2007	Ongoing	Severe	Remotely	No
Vaccines	0001	11927	SUICIDE ATTEMPT	27SEP2007	27SEP2007	Severe	Remotely	No
Vaccines	0001	12058	LEFT ANKLE FRACTURE	03OCT2007	Ongoing	Severe	Remotely	No
Vaccines	0002	20209	HERNIA	30MAR2007	31MAR2007	Severe	None	No
Vaccines	0002	20301	DEPRESSIVE DISORDER AND PSYCHOSIS	07FEB2007	09MAR2007	Severe	None	No
Vaccines	0002	20308	ALLERGIC REACTION TO PEANUTS	05FEB2007	06FEB2007	Severe	None	No
Vaccines	0002	20762	HEAD LACERATION	26SEP2007	27SEP2007	Severe	None	No
Vaccines	0002	20762	AUTO ACCIDENT	26SEP2007	27SEP2007	Severe	None	No
Vaccines	0002	20956	ABDOMINAL PAIN NOS	25JUN2007	28JUN2007	Severe	Remotely	No
Vaccines	0002	20956	PELVIC PAIN NOS	25JUN2007	28JUN2007	Severe	Remotely	No
Vaccines	0002	21334	ADJUSTMENT DISORDER W/DEPRESSED MOOD/ANXIETY	11AUG2007	17AUG2007	Severe	Remotely	No
Vaccines	0002	21447	CYCLOTHYMIC DISORDER	16AUG2007	24AUG2007	Severe	Remotely	No
Vaccines	0002	21447	PERSONALITY DISORDER	16AUG2007	24AUG2007	Severe	Remotely	No
Vaccines	0002	21505	ADJUSTMENT DISORDER	14SEP2007	17SEP2007	Severe	Remotely	No
Vaccines	0002	21505	SUICIDE THOUGHTS	14SEP2007	17SEP2007	Severe	Remotely	No
Vaccines	0002	21938	DEPRESSION NOS	08OCT2007	19OCT2007	Severe	Remotely	No
Vaccines	0002	21964	ADJUSTMENT DISORDER WITH DEPRESSED MOOD	04OCT2007	31OCT2007	Severe	Remotely	No
Vaccines	0002	22062	PAIN DUE TO ACUTE APPENDICITIS	31OCT2007	02NOV2007	Severe	Remotely	No
Placebos	0001	10338	LEFT RADIUS ULNA FRACTURE	10MAR2007	Ongoing	Severe	Remotely	No
Placebos	0001	10504	RIGHT LEG CELLULITIS	05MAR2007	15AUG2007	Severe	Remotely	No
Placebos	0001	10677	SUICIDAL ATTEMPT/DRUG INGESTION	05JUN2007	05JUN2007	Severe	Remotely	No

Treatment	Site	Subj	Serious AE (Verbatim)	AE Start	AE Stop	AE Severity	Causality	Discontinue
Placebos	0001	11074	FRACTURED LEG	20DEC2007		Severe	None	No
Placebos	0001	11686	RIGHT UPPER QUADRANT ABDOMINAL PAIN	26AUG2007	28OCT2007	Severe	Possibly	No
Placebos	0001	11686	SUICIDAL IDEATION	29OCT2007	05NOV2007	Severe	Remotely	No
Placebos	0001	12068	SUICIDAL ATTEMPT	14OCT2007	14OCT2007	Severe	Remotely	No
Placebos	0002	20224	FEBRILE ARD ASSOCIATED WITH VACCINE	13FEB2007	23JUL2007	Severe	Likely	No
Placebos	0002	20576	MAJOR DEPRESSION	26MAY2007	30MAY2007	Severe	Remotely	No
Placebos	0002	20693	BIPOLAR DISORDER	16MAY2007	07JUN2007	Severe	Remotely	No
Placebos	0002	20693	MIXED EPISODE WITH PSYCHOSIS	16MAY2007	07JUN2007	Severe	Remotely	No
Placebos	0002	20824	ADJUSTMENT DISORDER WITH ANXIOUS MOOD	13JUN2007	18JUN2007	Severe	Remotely	No
Placebos	0002	21036	ACUTE APPENDICITIS	18JUL2007	20JUL2007	Severe	Possibly	No
Placebos	0002	21247	DEPRESSED MOOD	26NOV2007	03DEC2007	Severe	None	No
Placebos	0002	21247	STRESS	26NOV2007	03DEC2007	Severe	None	No

†Reproduced from Table 31, BLA Section 5.3.5.1, page 65

Fifty-seven SAEs were reported in this study: 42 occurring in 36 of 3,031 (1.2%) subjects in the active vaccines group and 15 occurring in 13 of 1,009 (1.3%) subjects receiving placebo tablets.

One SAE of particular interest was the subject (20224) who had been randomized to receive placebo tablets and presented with febrile ARD. A throat specimen obtained from this subject was positive for ADV Type 4, vaccine strain. He is reported to have made a complete recovery. It is suspected that this case represents adenovirus infection and febrile ARD in a susceptible person secondary to viral shedding by a vaccinated person. No other similar cases were identified during the trial in the remaining 1,008 subjects vaccinated with placebo, despite careful surveillance.

Medical reviewer comment: In the judgment of this medical reviewer, subject 20224, a placebo recipient, represents the only case of an SAE definitively associated with the vaccine (discussed in more detail below). The vast majority of the SAEs listed in Table 36 likely were directly or indirectly due to the military basic training experience and could not be considered to be related to receipt of the vaccine.

Clinical case narratives for subject 20224, as well as for five others among vaccine recipients who developed SAEs that occurred during their participation in the study and that, in the judgment of the investigators, were “possibly” or “likely” related to receipt of the vaccine, are provided below. Case summary of Subject 10949, a reported case of severe acute bronchitis, and Subject 20956, a case reporting severe abdominal and pelvic pain, both assessed as “remotely” related to receipt of the vaccine by their respective clinical investigators, also are included below, given the relevance of the clinical presentation to the clinical symptoms associated with disease caused by ADV-4 or ADV-7 exposure.

Subject 20224 (Placebo recipient): Febrile ARD associated with Vaccine

Subject 20224 was a 21-year-old African American male, vaccinated with placebos on 10 January 2007. On the same day he also received the following vaccines: Adacel[®], Flumist[®], Menactra[®], MMR, IPOL[®], and Twinrix[®]. On 3 February 2007, the subject presented with symptoms of cough and intermittent productive cough. He had started erythromycin for those symptoms on 11 January 2007, but discontinued on 27 January 2007 without consulting medical staff. On 13 February 2007, the subject began to experience a sore throat, cough, nasal congestion, and chest congestion with a temperature of 101.3 °F. On the same day he was vaccinated with Typhoid polysaccharide, YF-VAX[®], and his second dose of Twinrix[®]. He was evaluated on 15 February 2007 and diagnosed with febrile ARD. Subsequently, the throat specimen was positive for adenovirus type 4, vaccine strain. The diagnosis was determined to be febrile ARD associated with vaccine (medically important and therefore serious, as well as severe and likely related to investigational product as per the investigator). He was treated with pseudoephedrine, Halls cough drops, acetaminophen, and Mucinex[®]. During the course of the study the subject also reported stuffy nose, pseudofolliculitis barbae to face, and vomiting. The subject completed the study and had the final study visit on 24 February 2007. He reported all symptoms were resolved with the exception of a remaining productive cough. The site made multiple attempts to contact the subject without success. Per his mother and military records, the subject recovered on 23 July 2007 and was doing well. He continued on active duty. The subject was considered lost to follow-up.

Medical reviewer's comment: This case likely represents an example of febrile ARD due to vaccine-strain ADV-4 occurring in a placebo recipient. This case illustrates the potential for transmission of the vaccine-strain viruses to susceptible individuals who come in close contact with vaccinees during the period of shedding (up to 28 days, as per shedding data from the Phase 1 study – see Section 8.1.2.5.4). The case serves as an important reminder that the vaccine strains are non-attenuated and are capable of causing disease to close contacts of vaccinees who are not immunologically protected. Limiting the indication of this vaccine to the military population at risk for ADV-4 and ADV-7 outbreaks is one strategy undertaken to limit risk of spread of the vaccine-strain viruses to the general population. Additionally, the risk management plans set forth by the applicant are designed to minimize the potential for spread to non-vaccinated contacts of vaccine recipients, particularly to those contacts, such as pregnant women, infants and immunocompromised individuals, where the consequences of such exposure may be more severe than in the general population.

Subject 10949 (Vaccine Recipient): Acute Bronchitis

Subject 10949 was a 19-year-old Caucasian female, randomized to active treatment and vaccinated on 15 May 2007. On the same day she also received the following vaccines: Adacel[®], Fluzone[®], Menomune[®], IPOL[®], Turbesol[®], and Vaqta[®]. During the course of the study the subject reported adverse events of cough, headache, stomach pain, bilateral elbow and knee joint pain, lower back pain, nausea, upper respiratory infection, and diarrhea; the patient had complained of cough, headache and stomach pain on the day of her vaccination. The subject completed the study and had the final study visit on 15 July

2007. The subject was found to have developed robust immune responses to both the ADV-4 and ADV-7 components of the vaccine (ADV-4 titer 1:181; ADV-7 titer 1:645.1 on Visit 3). On 17 July 2007, the subject presented to the clinic with chronic cough (non-productive) and congestion. She was diagnosed with acute bronchitis (serious, severe, and remotely related to investigational product as per the investigator) and sinusitis and treated with amoxicillin. She discontinued treatment after 2 days, at which time the symptoms worsened. The chronicity of her respiratory symptoms suggested pertussis in the assessment of one military medical officer. The patient experienced intermittent fevers; recurrent respiratory symptoms, including coughing and wheezing; and GI symptoms including hematemesis (she reported vomiting 2 teaspoonfuls of blood). She was diagnosed with esophageal reflux and reactive airway disease and treated with Reglan[®], and an albuterol inhaler. A chest x-ray on 18 September 2007 revealed no acute abnormality of the chest and the acute bronchitis was considered resolved.

Medical reviewer's comment: This case was included among those summarized here on the judgment of the medical reviewer, given the similarity of the symptoms with those that might be associated with ADV-4 or ADV-7 disease. It seems unlikely, however, that vaccine-associated ADV-4 or ADV-7 disease would manifest themselves two months following the receipt of the vaccine. Moreover, it is unlikely that the symptoms are due to acquisition of wild-type ADV-4 or ADV-7, given the negative throat culture and the robust immune responses manifest by the subject to the ADV-4 and ADV7 vaccine. While one individual who provided a medical assessment of this subject suspected pertussis, a precise cause of her respiratory symptoms never was established. Her symptoms ultimately resolved.

Subject 10996 (Vaccine Recipient): Gastroenteritis; Hematuria

Subject 10996 was a 19-year-old Caucasian male with a medical history that included kidney stones and an allergy to penicillin. The subject was randomized to active treatment and was vaccinated on 22 May 2007. On the same day he also received the following vaccines: Adacel[®], Fluzone[®], Menomune[®], IPOL[®], Twinrix[®] (repeated on 28 June 2007), and Turbesol[®]. On 30 May 2007, he presented to the clinic experiencing dizziness, nausea, vomiting, poor appetite, and leg pain due to a hamstring injury suffered in training on 25 May 2007. No treatment was documented and he was released. On 31 May 2007, the subject presented to the clinic with dizziness, chills, nausea, vomiting, sensory disturbance, vertigo, fatigue, right lower quadrant abdominal pain, body aches, and pain and muscle spasms in his left hamstring. His vital signs included blood pressure 131/73 mmHg, heart rate 62 bpm, respiratory rate 18 bpm, temperature 97.7 °F, and oxygen saturation 98%. On examination he had dry buccal mucosa, bilateral leg swelling, bilateral tenderness and weakness of the thighs, a normal abdominal examination, and left hamstring tenderness on palpation. Laboratory results, including hematology and chemistry panels, were unremarkable with the exception of AST 99 U/L (10-38), ALT 53 U/L (5-49), and creatinine kinase (CK) 2346 U/L (41-217). His elevated CK level was attributed to his pulled hamstring. A urinalysis was obtained and revealed a large amount of blood and red blood cells that were too numerous to count. The subject was treated with intravenous fluids, Phenergan[®], and Tylenol[®]. He was admitted to the hospital for observation and diagnosed with hematuria, gastroenteritis (both serious, severe, and

possibly related to investigational product as per the investigator), volume depletion, and dehydration. An abdominal and pelvic CT was performed and revealed free fluid in the pelvis and punctate right renal calculi with no evidence of ureterolithiasis, hydronephrosis, or calcifications in the bladder. On 1 June 2007, the subject reported improved symptoms with light headedness. His laboratory results, including urinalysis, were unremarkable with the exception of CK 1351 U/L (41-217). The hematuria was considered resolved. On 3 June 2007, his CK level was 306 U/L (41-217). A urinalysis was obtained and was normal. The gastroenteritis was considered resolved. On 4 June 2007, his CK level was 198 U/L (41-217) and his physical examination was normal. The subject completed the study and had the final study visit on 22 July 2007. On 9 August 2007, his laboratory results, including hematology and chemistry panels, were unremarkable.

Medical reviewer's comment: In the judgment of this medical reviewer, this case suggests the development of rhabdomyolysis. The assessment of "possible" causal association with the vaccine by the clinical investigator likely was made given the temporal association with the receipt of the vaccine (symptoms developed eight days following receipt of vaccine). While an association cannot be ruled out, it is also important to note that volunteers in this study were administered vaccine at the beginning of military basic training. Rhabdomyolysis is a known complication of intense physical exertion, particularly occurring during hot weather (these events occurred in late May and early June). No other such event was reported among vaccine or placebo recipients participating in this study.

Subject 11077 (Vaccine Recipient): Pneumonia

Subject 11077 was a 20-year-old Caucasian male with a medical history that included smoking, tonsillectomy, bipolar disorder, and allergies to guaifenesin, Lortab, and sulfa drugs. The subject was randomized to active treatment and was vaccinated on 4 June 2007. On the same day he also received the following vaccines: Adacel, Menomune[®], IPOL[®], and Twinrix[®]. On 15 June 2007, the subject began to experience sore throat, cough, rhinorrhea, achy body, and headache. On 17 June 2007 a throat culture was obtained for ADV 4 and ADV 7. The result of this culture was negative for both viruses. On 21 June 2007, he returned to the clinic and was diagnosed with severe ARD. A chest poster-anterior and lateral x-ray revealed a pattern that "closely resembled bronchitis." His treatment included Augmentin[®]. On 26 June 2007, the subject presented to the clinic with worsening cough, chills, fatigue, headache, and a temperature 101.2 °F. On examination he had an active cough without labored breathing, a "left lower lobe infiltrate," generalized pale skin, and musculoskeletal pain. He was admitted to the hospital on 27 June 2007 and diagnosed with pneumonia (serious, severe, and possibly related to investigational product as per the investigator). Laboratory results were unremarkable with the exception of white blood cells $15.7 \times 10^3/\text{mol}$ (4.5-11.5), red blood cells $4.3 \times 10^6/\text{mol}$ (4.6-6), hemoglobin 12.8 g/dL (14-18), hematocrit 37.5% (40-54), and lymphocytes 11.3% (20-50). A chest posterior-anterior and lateral x-ray revealed a "fairly extensive" bilateral lower lobe bronchopneumonia pattern, left greater than right, with a normal heart size. He was treated with intravenous fluids, Zithromax[®], and Rocephin[®]. On 28 June 2007, a chest posterior-anterior and lateral x-ray revealed slight interval

worsening in bibasilar pneumonias. He was also treated with Solu-Medrol[®] and Proventil[®]. On 3 July 2007, the pneumonia was improved and the subject was discharged to his unit with Levaquin[®]. On 12 July 2007, a chest posterior-anterior and lateral x-ray revealed improvement in bilateral lower lobe pneumonia with complete clearing on the right side and some residual slight infiltrate and pleural reaction on the left side. The subject reported complete resolution of his symptoms on 15 July 2007. The subject completed the study and had the final study visit on 5 August 2007. He was discharged from the military due to unrelated medical problems.

Medical reviewer's comment: The absence of throat culture evidence of ADV-4 or ADV-7 infection suggest that the infection experienced by this subject was not related to receipt of the vaccine.

Subject 11279 (Vaccine Recipient): Gastritis

Subject 11279 was an 18-year-old Caucasian female with a medical history that included a laparoscopic appendectomy on 5 June 2007, prior to beginning basic training. The subject was randomized to active treatment and was vaccinated on 23 July 2007. On the same day she also received the following vaccines: Adacel, Menomune, Turbesol, and Vaqta. On 15 August 2007, the subject presented to the clinic with complaints of constipation, hemorrhoids, emesis, and nausea. She reported seeing blood, 6 of the 7 times during emesis. She was treated with Fleet[®] enema, magnesium citrate, and Colace[®]. After treatment she had a bowel movement and reported blood in her stool. Her laboratory results were unremarkable with the exception of hemoglobin 11 g/dL (12-15) and hematocrit 33.5% (35-49). On 17 August 2007, the subject was admitted to the hospital with middle and right sided abdominal tenderness. She was diagnosed with gastritis (serious, severe, and possibly related to the investigational product as per the investigator). On 18 August 2007, the subject reported cough and heartburn. On 19 August 2007, the subject was discharged in stable condition and prescribed Aciphex[®] and Colace[®]. On 21 August 2007, the subject presented to the clinic for follow-up and was vomiting blood. On 22 August 2007, an upper gastrointestinal series was performed and no evidence of gastrointestinal bleeding was detected. On 24 August 2007, the subject presented to the clinic for her military physical medical evaluation. She reported abdominal pain, constipation, and dyspepsia. The subject was released to medical quarters ("self-care unit", where recruits are restricted to bed-rest and are seen daily by a health care provider until returned to duty). She reported that the gastritis resolved on 2 October 2007. The subject subsequently was diagnosed with an "adjustment disorder." The subject was discontinued from the study because she was discharged from the military on 7 October 2007. On 25 January 2008, the site attempted to contact the subject without success. The subject was considered lost to follow-up.

Medial reviewer's comment: While it may be theoretically possible that this orally-administered, live virus vaccine may have been the cause of this subject's symptomatology, it is difficult to make this assessment with any degree of certainty. The symptoms reportedly had resolved at the time of her premature discharge from the military.

Subject 11439 (Vaccine Recipient): Febrile Gastroenteritis

Subject 11439 was an 18 year old African American female. Urine pregnancy tests prior to enrollment to the study were negative. The subject was randomized to active treatment and was vaccinated on 6 August 2007. On 10 August the subject presented to the clinic with fatigue, nausea, vomiting, diarrhea, migraine, chills and a temperature of 101.6 °F. She was diagnosed with febrile gastroenteritis (serious, severe, and possibly related to the investigational product as per the investigator) and treated with normal saline, Reglan[®], ibuprofen and Tylenol[®]. The subject was discharged to the “self care unit.” On 11 August her GI symptoms had not improved and the subject returned to the clinic with a temperature of 102.5 °F. Laboratory results revealed a leukocytosis (wbc $17 \times 10^3/\text{mCL}$, anemia (hemoglobin 9.9 g/dL) and a urinary tract infection. She was treated with normal saline, Tylenol[®], morphine, Zosyn[®], Zofran[®], and Phenergan[®]. A qualitative pregnancy test was positive; a quantitative beta-HCG test was found to be 70 mIU/ml. Gestational age was approximately 3 weeks and 3 days. The estimated date of conception was 1 August 2007, 5 days prior to vaccination. On 12 August 2007 the subject was transferred to the hospital where abdominal and transpelvic ultrasounds revealed a right adnexal cystic mass consistent with a simple cyst or a ruptured corpus leuteum. No intrauterine pregnancy was noted; findings were consistent with either an ectopic or early pregnancy. An abdominal and pelvic CT revealed a slight thickening in the wall of the terminal ileum, consistent with an inflammatory process or infection (treatment regimen in hospital not specified). The subject was discharged on 13 August 2007 with prenatal vitamins and amoxicillin. On 19 August the subject was discontinued from the study due to her pregnancy and the treatment assignment was unblinded. The subject reported recovery from the “febrile gastroenteritis” on 19 September 2007. On 1 April 2008 the subject carried to term and vaginally delivered a healthy infant.

Medical reviewer’s comment: It is difficult to make an assessment of vaccine causality in this patient given the multiple possible etiologies of her symptoms, possibly exacerbated by her early pregnancy.

Subject 11794 (Vaccine Recipient): Hematochezia

Subject 11794 was a 22 year old Caucasian male with a family history that included ulcerative colitis. Several months prior to joining the military, he was admitted to the hospital for 10 days with abdominal pain and blood in his stool. At that time a colonoscopy was performed and revealed colitis. The subject was randomized to active treatment and was vaccinated on 10 September 2007. On the same day he also received the following vaccines: Adacel[®], Menomune[®], IPOL[®], Twinrix[®], and Turbesol[®]. On 22 October 2007, he was vaccinated with Flumist[®] and his second dose of Twinrix[®]. On 18 November 2007, the subject presented to the emergency room with periumbilical and left lower quadrant pain, abdominal swelling, abnormal perianal skin, nausea, and vomiting. He reported blood and blood clots in his stool beginning the evening of 17 November 2007 and 2 to 5 loose bowel movements a day for the past 10 days. He reported that over the past month concomitant medication included Motrin 800 mg tablets as needed. His laboratory results were unremarkable with the exception of red blood cells $4.1 \times 10^6/\text{mCL}$ (4.6-6), hemoglobin 12.7 g/dL (14-18), and hematocrit 36.6% (40-54). An abdominal x-ray was negative. He was diagnosed with hematochezia (serious, severe, and possibly

related to investigational product as per the investigator) and anemia. Medical records from his previous hospitalization were reviewed by the treating physician and indicated several biopsies obtained during colonoscopy revealed infectious colitis rather than inflammatory bowel disease. During that time, he was treated with antibiotics and improved. The subject completed the study and had the final study visit on 19 November 2007. On 20 November 2007, the subject was treated with Levaquin[®], Flagyl[®], and Bentyl[®]. On 23 November 2007, the subject was discharged from the hospital. It was reported that the subject fully recovered on 30 November 2007.

Medical reviewer's comment: While the patient's symptoms were assessed as possibly related to receipt of the vaccine by the clinical investigator, the patient's history of a non-specific inflammatory bowel disorder, existing prior to the receipt of the vaccine, makes an association with receipt of the vaccine seem unnecessary to invoke. While it may be possible to surmise that exposure to this live, oral vaccine may have exacerbated a pre-existing inflammatory bowel condition, the development of this subject's acute symptoms, more than two months following exposure to the vaccine, make this a less likely scenario.

Subject 20956 (Vaccine Recipient): Abdominal pain; pelvic pain

Subject 20956 was a 33-year-old Caucasian female with a medical history of easy bruising. The subject was randomized to active treatment and was vaccinated on 18 June 2007. On the same day she also received the following vaccines: Adacel[®], Flumist[®], Menactra[®], MMR, and Twinrix[®]. On 24 June 2007, the subject presented to the emergency room with generalized itching due to an allergic reaction and symptoms of abdominal and pelvic pain (both serious, severe, and remotely related to investigational product as per the investigator). Her physical examination revealed feet and genital swelling, lower extremity, lower abdominal, and vaginal bruising in various stages of healing. Her urinalysis revealed trace leukocytes and few bacteria. She was treated with Benadryl[®], Bactrim[®], acetaminophen, and loperamide. On 25 June 2007, the subject was admitted to the hospital for additional testing. Laboratory results were unremarkable with the exception of an elevated creatinine phosphokinase, elevated glutamic-oxalocetic transaminase, and mild macrocytic anemia. Her vaginal and cervical cultures revealed gram positive and negative cocci and rods. She was diagnosed with a urinary tract infection and vaginal infection. The subject was discharged from the hospital on 28 June 2007 and the events were considered resolved. At discharge, her creatinine phosphokinase was within normal limits. On 24 July 2007, laboratory tests were negative for Von Willebrand disease and there was no evidence of a bleeding disorder. The subject was released to full duty. The subject completed the study and had the final study visit on 1 August 2007. On 3 December 2007, the site attempted to contact the subject without success. The subject was considered lost to follow-up.

Medical reviewer's comment: While the clinical investigator assessed this case as "remotely" associated with receipt of the vaccine, the temporal association (symptoms developing within six days of vaccine administration) and the nature of the symptoms (an allergic-type rash and severe abdominal/pelvic pain) at least seem to raise the possibility that receipt of this oral, live virus vaccine may have been associated with

the clinical presentation, in the judgment of this medical reviewer. It may be that the urinary tract and vaginal infections were, in fact, the cause of these symptoms, but it is impossible to know. Importantly, the symptoms resolved within four days of onset.

Subject 22062 (Vaccine Recipient): Pain due to Acute Appendicitis

Subject 22062 was a 21 year old Caucasian male. He was randomized to active treatment and was vaccinated on 3 October 2007. On the same day he also received the following vaccines: Adacel[®], Menactra[®], MMR, and Twinrix[®]. On 31 October 2007, the subject presented to the emergency room with acute abdominal pain and emesis. He reported that the pain was generalized initially, but progressively localized to his right lower quadrant. On presentation he was afebrile with normal vital signs. On physical examination his right lower quadrant was tender to palpitation. Laboratory results were unremarkable with the exception of white blood cells 19.4 K/uL (4-11), neutrophils 88.2% (40-80) and 17.1 K/uL (1.5-5), and lymphocytes 6% (15-45). The subject was diagnosed with acute appendicitis (serious, severe, and remotely related to investigational product as per the investigator). He was admitted to the hospital on 1 November 2007 and treated with Mefoxin[®], hydromorphone, and ondansetron. On 2 November 2007, he was afebrile, experiencing no pain, and his white blood cell count was normal. The subject declined surgery and was discharged to training with Augmentin[®]. The event was considered resolved. The subject completed the study and had the final study visit on 17 November 2007.

Medical reviewer comment: While the clinical investigator assessed this event as “remotely” associated with receipt of the vaccine, the fact that this intra-abdominal event occurred within a month of vaccine exposure at least raises the question of a possible association, in the judgment of this medical reviewer.

8.1.2.5.3 Pregnancies

Five pregnancies were reported during this study. Subjects 10355, 11275, 11439, and 11580 were randomized to the vaccine group while Subject 11220 was randomized to the placebo group. Subject 11580 conceived approximately 21 weeks after she was vaccinated. The other subjects were estimated to have conceived 2–13 days prior to vaccination. Subject 11439’s pregnancy was identified approximately 10 days after conception and 5 days after vaccination when she presented with the SAE of febrile gastroenteritis (see above). The deliveries to all five pregnant subjects assigned to the vaccines arm were of healthy infants at estimated gestational ages between 36 4/7 and 39 5/7 weeks. The pregnant subject assigned to placebos delivered a healthy infant at 39 6/7 weeks of estimated gestational age.

8.1.2.5.4 Person to Person Shedding

One instance of likely person-to-person transmission of the vaccine strain ADV-4 virus occurred and was detailed in Section 8.1.2.5.2 (SAEs). In summary, Subject 20224 was a 21-year-old African American male, vaccinated with placebos on 10 January 2007. On 3 February 2007, the subject presented with symptoms of cough and intermittent productive cough. He was evaluated on 15 February 2007 and diagnosed with febrile ARD. Subsequently, the throat specimen was positive for ADV-4, vaccine strain. The diagnosis was determined to be febrile ARD associated with vaccine (medically important and therefore serious, as well as severe and likely related to investigational product as per the investigator). The subject completed the study and had the final study visit on 24 February 2007.

Although the Phase 3 study of the oral ADV 4/7 Vaccine safety and efficacy did not contain a formal study of adenovirus shedding, the Phase 1 study of the safety and immunogenicity of the vaccines in 58 individuals (30 vaccine recipients, 28 who received placebo) did include a study of viral shedding from the throat, and from fecal specimens. (The Phase 1 study is described in greater detail in Section 8.2.) In summary, throat swab specimens were collected from all treated subjects enrolled in this Phase 1 study at Study Days 0, 7, 14, 21, 28 and 56 and were tested for the presence of adenovirus. Only one throat swab sample (from subject (b)(6) in the placebo group at Day 7) was found to be positive for ADV-4 from subjects in the Phase 1 shedding study. This virus was found to be wild type by a PCR assessment.

Although swabs for ADV-4 and ADV-7 identification were not routinely obtained from participants in the Phase 3 study, they were obtained from individuals who developed signs and symptoms of ARD. No vaccine virus was detected in the throat swab specimens obtained from any subjects symptomatic for ARD participating in the Phase 3 study.

Fecal Cultures: Phase 1 Shedding Study

Fecal adenovirus shedding results obtained during the Phase 1 shedding study, stratified by pre-immunization antibody status at baseline (Day 0) for all treated subjects over time are summarized in Table 37. Adenoviruses other than ADV-4 or ADV-7 were not detected in the fecal samples.

Table 37: Adenovirus Isolation from Fecal Specimens by Treatment Group and Pre-Immunization Antibody Status over Time: All Treated Subjects[†]

STOOL VIRUS Type//Day	VACCINE Antibody (-) (+)/N	VACCINE Antibody (+) (+)/N	VACCINE Total (+)/N	PLACEBO Antibody (-) (+)/N	PLACEBO Antibody (+) (+)/N	PLACEBO Total (+)/N
Type4/Day 0	0/11	0/19	0/30	0/10	0/18	0/28
Type4/Day 7	7/11	0/18	7/29	1/10	0/17	1/27
Type4/Day 14	6/11	0/18	6/29	1/9	0/17	1/26
Type4/Day 21	1/11	0/18	1/29	0/9	0/17	0/26
Type4/Day 28	0/11	0/18	0/29	0/9	0/16	0/25
Type4/Day 56	0/11	0/18	0/29	0/9	0/16	0/25
Type4/Overall*	8/11	0/19	8/30	2/10	0/18	2/28
Type7/Day 0	0/17	0/13	0/30	0/14	0/14	0/28
Type7/Day 7	10/16	6/13	16/29	0/14	0/13	0/27
Type7/Day 14	5/16	3/13	8/29	0/13	0/13	0/26
Type7/Day 21	0/16	0/13	0/29	0/13	0/13	0/26
Type7/Day 28	0/16	0/13	0/29	0/13	0/12	0/25
Type7/Day 56	0/16	0/13	0/29	0/13	0/12	0/25
Type7/Overall*	12/17	6/13	18/30	0/14	0/14	0/28

*Subjects who tested positive at multiple time points were only counted once for overall

[†]Reproduced from Table 9.1, Phase 1 Study Report, BLA Section 5.3.4.1, page 48

Fecal ADV-4 and ADV-7 shedding was observed as early as Day 7. No fecal adenovirus shedding was detectable by Day 28 after vaccination.

Relationship of Baseline Adenovirus Immune Status to Fecal Viral Shedding in the Phase 1 Shedding Study:

Overall 8 of 30 (27%) subjects in the vaccine group tested positive at least once for ADV-4 fecal shedding from Day 0 to Day 56. Of the eleven vaccine recipients who were ADV-4 seronegative at baseline, eight (73%) had vaccine-strain ADV-4 detected in fecal specimens. In this Phase 1 study, nine (82%) of the eleven vaccine recipients who were ADV-4 seronegative at baseline seroconverted during their participation in the study. Eight (89%) of the nine seroconverters were found to be shedding vaccine-strain ADV-4. Additionally, the ninth ADV-4 seroconverter initially was reported as positive for fecal ADV shedding in a 48-hour culture using the shell vial method. Samples from this subject failed to show a positive result in a subsequent amplified tube culture and PCR assay on other fluid and therefore was classified as negative for fecal viral shedding on the final laboratory report. No ADV-4 fecal viral shedding was detected from any of the nineteen vaccine recipients found to be seropositive for ADV-4 at baseline.

Two placebo recipients were found to be shedding ADV-4 in fecal specimens. These ADV-4 isolates, however, were found to be wild-type, not vaccine strain.

Among the 30 ADV-7 vaccine recipients, eighteen (60%) were positive at least once for ADV-7 fecal viral shedding over the entire study period. Among these eighteen, twelve (67%) were among the seventeen subjects who were ADV-4 seronegative at baseline, while six (33%) were among the recruits who were ADV-7 seropositive at baseline. All six subjects from whom fecal ADV-7 was isolated were among the nine individuals in whom an antibody “booster effect” was noted, where this booster effect was defined as a four-fold increase or higher in a previously seropositive subject ($\geq 1:4$ at Day 0). (Nine

(69%) of thirteen vaccine recipients in this Phase 1 study manifest a booster effect to ADV-7. While a booster effect to ADV-4 was demonstrated in four (21%) of nineteen vaccine recipients, fecal specimens revealed no shedding of ADV-4 from these subjects.

Table 38 summarizes the correlation between fecal viral shedding and ADV-4 and ADV-7 serostatus.

Table 38: Correlation between Fecal Viral Shedding and Adenovirus Serostatus, Vaccine Recipients, Phase 1 Study[†]

Antibody Status, Day 0	Number of Subjects Vaccinated	Number of Seroconverters or Boosted Subjects	Fecal Viral Shedding	Fecal shedders/ seroconverters–or boosted subjects (%)
Type 4 (-)	11	9 seroconverters	8* positive	8/9 (89%)
Type 4 (+)	19	4 boosted	0 positive	
Type 7 (-)	17	12 seroconverters	12 positive	12/12 (100%)
Type 7 (+)	13	9 boosted	6 positive	6/9 (67%)

[†]Reproduced from Table 9.2, Phase 1 Study Report, BLA Section 5.3.4.1, page 49

An assessment of shedding of the Wyeth ADV-4 vaccine also was performed (Edmonson, et al., 1966). In this study of 104 individuals, randomized 1:1 to receive the Wyeth ADV-4 vaccine or placebo, respectively, ADV-4 was recovered from anal swab specimens from all 37 vaccine recipients whose ADV-4 neutralizing antibody titers were ≤1:4 at baseline, and from seven of fifteen vaccine recipients whose ADV-4 neutralizing antibody titers were >1:4 at baseline. ADV-4 was not recovered from any throat specimens, however, indicating that vaccine induced enteric infection did not spread to the upper GI tract or the respiratory tract where symptomatic infection could occur. Furthermore, ADV-4 did not spread to susceptible individuals in the placebo group who came in close personal contact with the vaccinated subjects throughout basic training, even though the ADV-4 vaccine virus continued to be shed by the vaccinated volunteers over a 16-day interval.

8.1.3 Comments and Conclusions

The safety, clinical and immunogenicity data from this study support the approval of a single dose of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, consisting of individual doses of ADV-4 and ADV-7, for the prevention of febrile ARD caused by these adenovirus strains in U.S. military recruits.

8.1.3.1 Study Design and Implementation

The protocol-defined endpoints were clear and appropriate. Review of the data did not identify any concerns with trial implementation. The quality of the data appear to be acceptable. The statistical conclusions reached by the applicant appear to be credible and well supported by the data.

8.1.3.2 Clinical Efficacy (Adenovirus Type-4 Vaccine)

The ADV4 vaccine surpassed pre-specified efficacy criteria for the primary clinical endpoint: prevention of febrile ARD due to ADV Type-4. In the ITT cohort, only one subject who received the ADV-4 vaccine developed febrile ARD caused by wild ADV-4, compared to the development of febrile ADV-4 ARD in 48 subjects who received placebo, resulting in a vaccine efficacy estimate of 99.3%, greater than the pre-specified 80% determinant of efficacy. The lower bound of the 95% confidence interval for this result was 96.0% for vaccine efficacy, which is greater than the 60% lower bound for the 95% CI established as a predetermined threshold for determining efficacy.

As the protective effect of the vaccine is unlikely to develop during the first 10 days following vaccination, an analysis of febrile wild ADV-4 ARD cases occurring more than 10 days following vaccination was undertaken. A total of 44 such ARD cases were observed; all 44 cases occurred in the placebo group. The VE estimate was 100%, supporting the claim that the adenovirus vaccine is efficacious in reducing wild ADV4 febrile ARD cases.

8.1.3.3 Immunogenicity

The primary effectiveness endpoint for the ADV-7 vaccine component was ADV-7 seroconversion at week 4 post-vaccination, given the low incidence of respiratory disease due to ADV-7 in this population. In the ITT cohort, the ADV-7 seroconversion rate was 93.8%, which is greater than the pre-specified efficacy threshold of 75%. The lower bound of the 2-sided 95% CI was 92.4%, greater than the pre-specified 70% efficacy threshold.

For ADV-4, the seroconversion rate at week 4 was 94.5%, with a lower bound for the 95% CI of 93.4%. This high rate of seroconversion correlated well with the clinical efficacy results reported for this vaccine.

All pre-specified primary immunogenicity endpoints for lot consistency of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral were met.

8.1.3.4 Safety

The types and frequency of the most commonly reported treatment-emergent and treatment-related AEs (those reported by $\geq 1\%$ of subjects) were similar between vaccine and placebo recipients, whether they were solicited or unsolicited (Tables 26 - 30).

There were no deaths in the study. SAEs were reported in 1.2% of subjects receiving the active vaccines and 1.3% of those receiving placebos. Only one reported SAE was described as *likely* to have been caused by the vaccine. This occurred in a placebo recipient, subject 20224, who presented with febrile ARD and whose throat specimen was positive for ADV-4, vaccine strain. He is reported to have made a complete recovery. It is suspected that this case represents adenovirus infection and febrile ARD in

a susceptible person secondary to viral shedding by a vaccinated person. Although no other similar cases were identified during the trial in the remaining 1,008 subjects vaccinated with placebo despite careful surveillance, this case illustrates both the potential of febrile ARD developing due to exposure to virus shed from vaccine recipients, and the clinical consequences of ARD due to ADV-4 occurring in unvaccinated individuals.

The Phase 1, placebo-controlled, double-blind safety and immunogenicity study of the co-administered Duramed ADV-4 and ADV-7 vaccines, conducted during the autumn of 2004, also supported the safety of these vaccines (this study is presented in greater detail in Section 8.2). Fifty-eight persons were enrolled in this study; 30 receiving the vaccines and 28 receiving placebo. Five SAEs were reported. Two of these SAEs (appendicitis in the vaccine group and right thigh abscess in the placebo group) were reported at the 6-month follow-up. The other three SAEs were reported up through Day 56: one subject in the vaccine group had pneumonia, with negative throat cultures for ADV; one subject in the placebo group had pneumonia and another subject in the placebo group had upper respiratory infection (URI), with positive throat cultures for wild ADV-4. No subjects discontinued the study due to AEs. Three placebo group subjects (including the two previously mentioned SAE subjects with pneumonia and URI) had throat swab samples positive for wild type ADV-4, but not for vaccine ADV-4. Individuals who received the active vaccines reported a greater incidence of abdominal pain (n = 5; 16.7%) and diarrhea (n = 4; 13.3%) than did individuals who received placebo (abdominal pain: n = 1; 3.6%, diarrhea: n = 2; 7.1%). These symptoms only appeared in the first week following receipt of vaccine/placebo and were graded as mild to moderate.

8.1.3.5 Safety Conclusions

The safety data in the BLA support the approval of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral to prevent febrile acute respiratory disease due to ADV-4 and ADV-7 in military recruits.

8.2 Phase 1 Study

8.2.1 Applicant's Protocol Number and Protocol Title

Study DR-ADV-101: A phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy and immunogenicity of the live, oral type-4 and type-7 adenovirus vaccines

Reviewer's note: This was the sole Phase 1 study which enrolled a relatively small number of individuals (n = 58) as compared to the Phase 3 study reviewed above. The critical additional information provided by this study addressed the question of the duration of adenovirus shedding following the administration of the ADV-4 and ADV-7 vaccines. Accordingly, the review of this study will be limited and will focus upon the shedding data.

8.2.1.1 Objective/Rationale

The primary objective of this study was to evaluate the safety of the ADV-4 and ADV-7 oral adenovirus vaccines administered together in healthy subjects who were seronegative for either one or both ADV-4 and ADV-7 at baseline, compared to a similar group of healthy subjects randomized to placebo. Secondary objectives were to evaluate the immune response (neutralizing antibody and seroconversion rate) to the ADV-4 and ADV-7 vaccines, and to characterize the duration of vaccine virus shedding in stool and throat secretions in vaccine recipients.

8.2.1.2 Design Overview

This was a randomized, double-blind, parallel, placebo-controlled study of the combined ADV-4 and ADV-7 vaccines in healthy soldiers, ages 18 to 40. A total of 60 eligible subjects (30 per group) who did not have a pre-existing adenovirus titer (i.e., $\leq 1:4$) to at least one adenovirus serotype (4 or 7) were to be enrolled. Subjects determined to be eligible and available for enrollment were randomly assigned in a 1:1 ratio to either vaccine or placebo treatment using a block size of four and stratified by ADV-4 and ADV-7 status at screening. Randomization was stratified to ensure that the treatment groups reflected the following target characteristics and that an adequate number of subjects with the following serotypes would be studied: seronegative to both ADV-4 and ADV-7, seronegative to ADV-4 and seronegative to ADV-7. This was done by including at least fifteen subjects per treatment group (vaccine and placebo) who were seronegative to ADV-7 at baseline (Day 0) and at least fifteen subjects per treatment group (vaccine and placebo) who were seronegative to ADV type 4 at baseline (Day 0). A subject who was seronegative at baseline to both ADV-4 and ADV-7, when randomized, would have been counted as satisfying the criterion for the fifteen subjects per treatment group criterion for both the ADV-4 stratum and the ADV-7 stratum.

8.2.1.3 Population

Inclusion Criteria:

- Healthy adults, 18 to 40 years of age, inclusive, at time of study medication administration
- Robust health, as assessed by the principal investigator, based on medical history, PE and screening laboratory test results
- Written informed consent
- Availability for the full study duration, and willingness to meet the specimen collection schedule
- For female subjects, non-childbearing potential (i.e., surgically sterilized or 1 year post-menopausal) or, if of childbearing potential negative urine pregnancy test prior to study medication administration with an agreement not to become pregnant during the study and for the 30 days after the last study visit on Day 56. The subject must not have been nursing an infant during the duration of the study and for 30 days after the last study visit on Day 56.

- No adenovirus antibody titer (i.e., at screening) to ADV-4 and to ADV-7 adenovirus, OR only titer to ADV-4 OR ADV-7 at $\leq 1:4$ as determined by the colorimetric microneutralization test.

Exclusion Criteria:

- Exclusion criteria were presented in the BLA submission, were reviewed, and were judged to be appropriate for this study. Importantly, subjects with antibodies to ADV-4 and ADV-7 were excluded from participation. Other important exclusion criteria included an immunosuppressive state, a history of previous live, vaccine within the 30 days prior to study medication administration or the use of any vaccine from 30 days prior to study medication administration to the end of the study period.

8.2.1.4 Products Mandated by the Protocol

Dosage and Administration of Study Vaccines:

This was a one-time dose regimen. Each treatment consisted of two enteric-coated tablets, administered orally, kept in the mouth as briefly as possible, and swallowed with water without chewing. Tablets were administered simultaneously (within five minutes of each other). Study personnel observed the ingestion and oral cavities of subjects were observed afterwards by study personnel to document that the tablets had been swallowed.

Treatments Administered:

- Live oral Type 4 adenovirus vaccine tablet (ADV-4) (Lot #F4A023015A)
 - Live oral Type 7 adenovirus vaccine tablet (ADV-7) (Lot #E4A023014A)
- Or
- Matching ADV-4 placebo tablet (Lot #G4A023016A) and
 - Matching ADV-7 placebo tablet (Lot #G4A023017A)

Formulation of Study Vaccines:

Each oral tablet contained not less than 32,000 tissue culture infectious doses (TCID) of ADV-4 or ADV-7. The vaccines used the same master seeds, and were grown in the same cell substrate (WI-38 human diploid fibroblast cells) as were used for the previously licensed Wyeth ADV-4 and ADV-7 vaccines.

8.2.1.5 Endpoints

8.2.1.5.1 Primary Efficacy Endpoints

The primary efficacy endpoints were as follows:

- Seroconversion rates at Day 28
- Viral shedding through Day 56

The definition of seroconversion and the neutralizing assay used to determine seroconversion were as described for the Phase 3 study.

Viral shedding was measured as positive or negative for detecting ADV-4, ADV-7 and other types from cultures of stool samples or rectal swabs and throat swabs on Days 0, 7, 14, 21, 28 and 56. If the result of throat swab culture showed positive for ADV-4 or ADV-7, then a PCR analysis was conducted to further determine whether the virus was vaccine or wild type.

8.2.1.5.2 Safety Endpoints

The primary safety endpoints were a description of adverse events based on clinical laboratory evaluations (blood chemistry, hematology, urinalysis), vital signs, incidence of viremia, and physical examination. Safety was evaluated by assessment of serious adverse events, adverse events, historical and concomitant medications, physical exams, vital signs, clinical labs, viremia and a seven day symptom diary.

Adverse events included the time and description of a single AE. Severity was categorized as one of the following: mild, moderate or severe. Relationship to study medication was categorized as none, remote, possible, likely or definitely. AEs also were designated as serious or not serious as per the investigator's judgment. SAEs that occurred during this trial were reported to the applicant's medical monitor and subsequently were submitted to the FDA.

Information on concomitant medications was recorded on the case report form (CRF) at each visit. Physical examinations occurred at the baseline visit and at any of the follow-up visits if symptoms of adenovirus infection were identified. Vital signs were taken at all visits.

A complete blood count (CBC) and chemistry panel was obtained at the screening visit and at the last visit (Day 56). More directed clinical labs included only a CBC, creatinine (CR) and alanine aminotransferase (ALT) and were taken at the baseline visit (Day 0), and at the Day 7, Day 21 and Day 28 visits.

Viremia was reported as positive or negative test results for adenovirus type 4, type 7 or other serotypes from blood samples taken on Days 0, 7, 14, 28 and 56.

A seven day symptom diary solicited information on headache, fever, cough, diarrhea, nausea, stuffy nose, sore throat, abdominal pain, abdominal cramping, and vomiting. Symptoms were scored as 1, 2, or 3 where 1 equaled unnoticed, 2 equaled little effect on daily activities and 3 equaled large effect on daily activities. The time of each symptom onset and the time resolved or still ongoing were recorded as well. These variables were recorded daily from Day1 to Day 7 after vaccination.

8.2.1.6 Statistical Considerations

8.2.1.6.1 Sample Size/Statistical Power

Sample size considerations for this Phase 1 study primarily were based on considerations regarding calculation of seroconversion rates (the secondary endpoint of the study) given that the primary endpoint of this study was safety, for which sample size primarily is a function of what is considered clinically reasonable for a Phase 1 study. Sample size calculations suggested that there would be little change in the lower 95% CI boundary by varying the group size between 20 and 40 (Table 39). Accordingly, a sample size of 30 vaccine subjects per group (vaccine or placebo recipients) was selected, with at least 15 ADV-4 seronegative and 15 ADV-7 seronegative subjects in each group.

Table 39: Lower 95% Confidence Boundaries for Given Proportions of Subjects Having Seroconversion and the Number of Subjects per Treatment Group[†]

% Seroconversion	N=10	N=20	N=25	N=30	N=35	N=40
70%	36%	46%	50%	51%	53%	53%
80%	44%	56%	59%	61%	63%	64%
90%	56%	68%	73%	74%	76%	76%

[†]Reproduced from Table 2, BLA Section 5.3.4.1, p.33

8.2.2 Results

8.2.2.1 Populations Enrolled/Analyzed

8.2.2.1.1 Study Sites and Study Period

Subjects were enrolled at the Army Medical Department Center and School, Fort Sam Houston, TX. The period of the study ranged from 14 August 2004 to 24 April 2005.

8.2.2.1.2 Subject Disposition and Follow-up

The disposition of subjects by treatment is presented in Table 40.

Table 40: Disposition of Subjects by Treatment[†]

Disposition	Vaccine N	Vaccine %	Placebo N	Placebo %	Total N	Total %
Screened	-	-	-	-	407	-
Randomized	35	-	38	-	73	-
Treated (Day 0)	30	100.0	28	100.0	58	100.0
Completed Day 28 (Seroconversion)	29	96.7	25	89.3	54	93.1
Completed Day 56 (Last Visit)	29	96.7	25	89.3	54	93.1
Day 180 follow-up	18	62.1	14	56.0	32	59.3

[†]Reproduced from Table 3.1, BLA Module 5.3.4.1, p.36

A total of 407 subjects were screened for ADV antibody titer at the screening visit. Only subjects seronegative to either or both ADV-4 and ADV-7 were eligible to enter the study. Of the 407 screened, 73 were randomized in a 1:1 ratio to either the vaccine or placebo group. On the immunization day (Study Day 0), 60 of the 73 subjects presented for dosing. Two of the 60 subjects had a fever and therefore were not dosed.

8.2.2.1.3 Subject Demographics

Demographic and vital sign information at baseline is summarized in Table 41. Among the 58 treated subjects, 69% were Caucasian, approximately 16% were Hispanic, non-white and 7% were African American. Seventy-six percent of the subjects were males. The median age of all treated subjects was 19 years.

Table 41: Demographic Information at Baseline⁺

DEMOGRAPHIC	VACCINE (N=30)	PLACEBO (N=28)	TOTAL (N=58)
RACE - African-American	3 (10.0%)	1 (3.6%)	4 (6.9%)
RACE - Asian	0	0	0
RACE - Caucasian	23 (76.7%)	17 (60.7%)	40 (69%)
RACE - Hispanic, White	0	2 (7.1%)	2 (3.4%)
RACE - Hispanic, Non-White	4 (13.3%)	5 (17.9%)	9 (15.5%)
RACE - Other	0	0	0
GENDER - Male	22 (73.3%)	22 (78.6%)	44 (75.9%)
GENDER - Female	8 (26.7%)	6 (21.4%)	14 (24.1%)
AGE - Mean (SD)	20.0 (2.57)	21.1 (3.99)	20.6 (3.35)
AGE - Median	19.0	19.5	19.0
AGE - (Min, Max)	(18.0, 28.0)	(18.0, 26.0)	18.0, 26.0)

⁺Adapted from Table 4, BLA Section 5.3.4.1, page 40

The slight differences in race and gender between the two treatment groups were not unexpected given the small sample size.

8.2.2.1.4 Antibody Status at Baseline (Day 0)

Subjects were screened for ADV-4 and ADV-7 serum neutralizing antibody status at the screening visit. Seronegative was defined as an antibody titer <1:4. Seropositive was defined as an antibody titer ≥1:4. Only persons seronegative to either one or both types were eligible for randomization. During the screening period (up to 44 days), however, some subjects developed neutralizing antibody and their antibody status changed from negative to positive before immunization.

At the screening visit, 33 subjects out of 58 were seronegative to ADV-4, while on the day of immunization (Day 0), only 21 of the 58 were seronegative to ADV-4, meaning that 12/33 (36.4%) subjects, six in the vaccine group and six in the placebo group, who were ADV-4 seronegative at the screening visit became seropositive at Day 0 before they were vaccinated. These data suggest that a natural background of ADV-4 infection existed during the screening period.

A total of 31 subjects out of 58 were seronegative to ADV-7 at the screening visit. No ADV-7 seronegative individual was found to have seroconverted to ADV-7 seropositivity at the time of immunization. Further examination, however, revealed that four subjects who initially were determined to be ADV-7 seronegative at screening became seropositive at Day 0 and four other subjects who were ADV-7 seropositive at screening became negative at Day 0. Because most of these changes in serostatus involved marginal changes in assay titer, and because it was unlikely that wild-type ADV-7 was circulating in the period between screening and initial immunization, it is likely that these changes in serostatus resulted from a small degree of variability in the assay.

8.2.2.1.5 Treatment Compliance

All treated subjects ingested their study medication at the baseline visit (Day 0).

8.2.2.2 Primary Efficacy Endpoints

8.2.2.2.1 Primary Efficacy Endpoint: Seroconversion

Seroconversion at Day 28:

Day 28 ADV-4 and ADV-7 seroconversion data are shown in Table 42.

Table 42: Day 28 Seroconversion Rate and 95% Confidence Interval[†]

ADV Type	Vaccine Converted	Vaccine N*	Vaccine %	Vaccine 95% CI**	Placebo Converted	Placebo N*	Placebo %	Placebo 95% CI**
ADV-4	8	11	72.7	(39.0, 94.0)	3	9	33.3	(7.5, 70.1)
ADV-7	10	16	62.5	(35.4, 84.8)	0	13	0.0	(---, ---)

*N = total number of subjects who were ADV-4 or ADV-7 seronegative at Day 0 and whose Day 28 titer was not missing

** 95% CI was calculated using exact binomial method

[†]Reproduced from Table 7.1, BLA Module 5.3.4.1, p. 44

For ADV-4, of the eleven subjects in the vaccine group who were ADV-4 seronegative at Day 0 and who provided ADV-4 titer data for Day 28, eight (72.7%) had a 4-fold rise in titer and therefore were considered to have seroconverted. The lower bound of the 95% CI for ADV-4 seroconversion at Day 28 among vaccinees was 39%. For the placebo group, three of nine (33.3%) subjects seroconverted. The lower bound of the 95% CI for seroconversion at Day 28 among placebo recipients was 7.5%. The three ADV-4 placebo subjects who seroconverted all were shown to have been exposed to wild-type ADV-4 infection via viral cultures obtained from throat swabs.

For ADV-7, of the 16 subjects in the vaccine group who were ADV-7 seronegative at Day 0 and who provided ADV-7 titer data for Day 28, ten (62.5%) seroconverted at Day 28. The lower bound of the 95% CI for ADV-7 seroconversion at Day 28 among vaccinees was 35.4%. For the placebo group, none of the 13 subjects seroconverted.

Cumulative Seroconversion Over Time:

The cumulative seroconversion rates across Day 7, Day 14, Day 28 and Day 56 is set forth in Table 43. In this analysis, any subject who seroconverted on or prior to Day 56 is carried forward to all visits up to and including Day 56.

Table 43: Cumulative Seroconversion by Treatment Group over Time⁺

Cumulative Seroconversion Type/Day	VACCINE (N* = 11) Seroconverted	VACCINE (N* = 11) %	PLACEBO (N* = 10) Seroconverted	PLACEBO (N* = 10) %
ADV-4/Day 7	0	0	0	0
ADV-4/Day 14	6	54.5	2	20.0
ADV-4/Day 28	8	72.7	3	30.0
ADV-4/Day 56	9	81.8	3	30.0
ADV-7/Day 7	0	0	0	0
ADV-7/Day 14	10	58.8	0	0
ADV-7/Day 28	11	64.7	0	0
ADV-7/Day 56	12	70.6	0	0

⁺Adapted from Table 7.2, BLA Section 5.3.4.1, page 45

For both ADV-4 and ADV-7 vaccines, seroconversion first was observed beginning on Day 14. For ADV-4, the cumulative seroconversion rate by Day 14 was 54.5% for the vaccine group vs. 20.0% for the placebo group. By Day 28, two more subjects in the vaccine group and one more subject in the placebo group had seroconverted, with cumulative seroconversion rates for ADV-4 of 8 out of 11 (72.7%) for the vaccine group vs. 3 out of 10 (30.0%) for the placebo group. By Day 56, the cumulative seroconversion rate for ADV-4 was 81.8% for the vaccine group vs. 30.0% for the placebo group.

For ADV-7 vaccine, 10 of 17 (58.8%) in the vaccine group had seroconverted by Day 14 while no seroconversions occurred in the placebo group. By Day 28, the seroconversion rate in the vaccine group had increased to 64.7% and by Day 56 it had increased to 70.6%. None of the ADV-7 placebo recipients seroconverted at any study visit.

8.2.2.2 Primary Efficacy Endpoint: Viral Shedding

Adenovirus Isolation from Throat Swab Specimens:

Throat swab specimens were collected for all treated subjects at Study Days 0, 7, 14, 21, 28 and 56 and were tested for the presence of adenovirus. Only one sample, obtained from a subject (subject no. (b)(6) in the placebo group at Day 7, was found to be positive for ADV type 4 virus, during a routine, prespecified throat swab assessment. This isolate was determined to be a wild-type ADV-4 by PCR analysis.

Positive throat culture results also were found during the ARD work-up procedure for two subjects with reported SAEs. Subject no. (b)(6) reported an acute upper respiratory infection (URI) on Day 12 and subject no (b)(6) reported pneumonia as an SAE on Day 10. Both subjects were in the placebo group and had a throat swab done at the time of presentation or hospital admission. In both cases, virus isolation from the throat was determined to be wild-type ADV-4. (NB: Subjects Nos. -----(b)(6)----- were the same three subjects who had a positive ADV-4 seroconversion in the placebo group.)

No vaccine virus was detected in the throat swab specimens from any treated subjects.

Adenovirus Shedding from Fecal Specimens:

The fecal viral shedding results by treatment group, stratified by pre-immunization antibody status at baseline (Day 0) for all treated subjects over time, is presented in Table 44. Adenoviruses other than types 4 and/or 7 were not detected in the fecal samples.

Table 44: Adenovirus Isolation from Fecal Specimens by Treatment Group and Pre-immunization Antibody Status over Time: All Treated Subjects[†]

Stool Virus Type/Day	Vaccine Antibody (-) (+) / N	Vaccine Antibody (+) (+) / N	Vaccine Total (+) / N	Placebo Antibody (-) (+) / N	Placebo Antibody (+) (+) / N	Placebo Total (+) / N
Type4/Day 0	0 / 11	0 / 19	0 / 30	0 / 10	0 / 18	0 / 28
Type4/Day 7	7 / 11	0 / 18	7 / 29	1 / 10	0 / 17	1 / 27
Type4/Day 14	6 / 11	0 / 18	6 / 29	1 / 9	0 / 17	1 / 26
Type4/Day 21	1 / 11	0 / 18	1 / 29	0 / 9	0 / 17	0 / 26
Type4/Day 28	0 / 11	0 / 18	0 / 29	0 / 9	0 / 16	0 / 25
Type4/Day 56	0 / 11	0 / 18	0 / 29	0 / 9	0 / 16	0 / 25
Type4/Overall*	8 / 11	0 / 19	8 / 30	2 / 10	0 / 18	2 / 28
Type7/Day 0	0 / 17	0 / 13	0 / 30	0 / 14	0 / 14	0 / 28
Type7/Day 7	10 / 16	6 / 13	16 / 29	0 / 14	0 / 13	0 / 27
Type7/Day 14	5 / 16	3 / 13	8 / 29	0 / 13	0 / 13	0 / 26
Type7/Day 21	0 / 16	0 / 13	0 / 29	0 / 13	0 / 13	0 / 26
Type7/Day 28	0 / 16	0 / 13	0 / 29	0 / 13	0 / 12	0 / 25
Type7/Day 56	0 / 16	0 / 13	0 / 29	0 / 13	0 / 12	0 / 25
Type7/Overall*	12 / 17	6 / 13	18 / 30	0 / 14	0 / 14	0 / 28

[†]Reproduced from Table 9.1, BLA Section 5.3.4.1, page 48

Among a total of 30 subjects in the vaccine group, the number who had ADV-4 shedding in fecal specimens was none at Day 0, seven at Day 7, six at Day 14, one at Day 21 and none at Days 28 and 56. The number who had ADV-7 shedding was one at Day 0, sixteen at Day 7, eight at Day 14, and none at Days 21, 28 and 56. Accordingly, fecal ADV shedding was observed as early as Day 7, while no shedding was observed by Day 28 after vaccination.

Overall, eight (26.7%) out of 30 subjects in the vaccine group tested positive at least once for ADV-4 fecal shedding from Day 0 to Day 56. All eight had demonstrated seroconversion at Day 28. The one additional ADV-4 seroconverter (subject no. (b)(6)) had a fecal specimen initially reported as positive for fecal ADV shedding in a 48-hour culture, but failed to show a positive result in a subsequent amplified tube culture and PCR assay on the culture fluid and therefore was classified as negative for fecal viral shedding in the final lab report.

For the ADV-7 vaccine group, 18 (60%) out of 30 subjects were positive at least once for ADV-7 fecal viral shedding over the entire study period.

8.2.2.3 Comments and Conclusions

This Phase 1 trial demonstrated sufficient immunogenicity to lead to the definitive, Phase 3 trial, as describe in Section 8.1, above. The key additional information provided by this trial came from the analysis of ADV-4 and ADV-7 shedding. As detailed in Section 8.2.2.2.2, above, no vaccine-strain virus was identified from any throat swab material obtained from vaccine or placebo recipients at any study visit, including Day 0, when the vaccine was administered. This result suggests that the tablets, when not chewed, remain intact upon ingestion long enough to prevent exposure of the oral cavity to the live ADV-4 and ADV-7 contained in the core of the respective vaccine tablets.

In contrast, vaccine-strain virus could be identified from fecal samples obtained as far out as 21 days (for ADV-4) and 14 days (for ADV-7) from vaccine recipients. All shedding appeared to have ceased, however, by Day 28 following vaccination. This information provided the basis for the risk-management plan designed to minimize potential exposure to vaccine-strain virus among civilians should the military recruits for whom this vaccine will be indicated be discharged from the military within 28 days of receipt of vaccine.

9. Additional Clinical Issues

9.1 Directions for Use

The proposed directions for use (oral administration as two tablets, one tablet of Adenovirus Type 4 and one tablet of Adenovirus Type 7, swallowed whole and not chewed or crushed) is consistent with use in clinical trials.

9.2 Dose Regimen

The proposed dose regimen (oral administration as two tablets, one tablet of Adenovirus Type 4 and one tablet of Adenovirus Type 7, swallowed whole and not chewed or crushed) is consistent with use in clinical trials and is supported by the available data.

9.3 Special Populations

9.3.1 Pediatrics

Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is intended for use in military personnel, primarily military recruits, for prevention of acute febrile respiratory disease due to ADV-4 and ADV-7. Accordingly, this product is not intended for use in individuals below the age of conscription (i.e., <17 years of age).

Teva Women's Health, Inc. is requesting a full waiver of pediatric studies pursuant to 21 CFR 314.55, section (c)(2) pertaining to the following:

- (i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;
- (ii) Necessary studies are impossible or highly impractical because the number of such patients is so small or geographically dispersed; or
- (iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

In defense of their request for a waiver of pediatric studies, the applicant notes that there are 51 serotypes of human adenoviruses which are associated with a broad spectrum of diseases (Wong 2008). Historically, adenovirus serotypes 1, 2, 3, and 5 have been most frequently associated with respiratory infections in children, followed by serotypes 6 and 7 (Brandt 1969, Mitchell 2000).

Adenovirus-associated respiratory disease has been well documented in U.S. military populations, but there is little information on its occurrence in other healthy populations, including pediatric groups. The applicant notes that, although ADV-4 and ADV-7 have found an ecological niche among U.S. military recruits in training, there does not appear to be sufficient evidence to suggest that adenovirus infections with these adenovirus serotypes pose a serious, enduring threat to the pediatric community that would warrant the use of live, oral vaccines.

Recent North American data demonstrates that the highest rate of all ADV infections as detected by PCR occurs among children between the ages of six months to six years (Wong 2008). During the past 25 years, however, there have been no reported widespread outbreaks of respiratory disease cause by ADV-4 or ADV-7 in children in the U.S. The applicant notes that there have been 3 isolated disease outbreaks in children related to ADV-7 described in the literature:

1) July 1982: At a chronic care pediatric hospital in Pennsylvania, four (29%) of fourteen children developed an acute respiratory illness characterized by upper or lower respiratory tract infection, fever, and respiratory distress due to ADV-7. Of these four symptomatic cases, three had lower respiratory tract infections which required mechanical ventilation. Two died. Three asymptomatic cases of ADV-7 among the pediatric patients also were diagnosed, as well as documented ADV-7 infection in two of the 35 staff members. The presumed index source was a staff physician with conjunctivitis and an upper respiratory tract infection. (CDC 1983)

2) March 1 – July 27, 1997: ADV infection was identified in 51 samples from 47 hospitalized children in a 225 bed facility which served as the only pediatric hospital in the region (the hospital was not identified, although the facility likely was in or nearby to Tennessee, given that the authors all were from Tennessee, including some from the TN Department of Health). Twenty-six of the 47 cases were confirmed to be ADV-7 (ages 11 days to 4 years). Two of the cases were considered to be nosocomially acquired. Twenty-four of the 26 patients had respiratory symptoms. There were no reported deaths (Mitchell 2000).

3) September – October 1998: Thirty-one of 93 mentally disabled children at a Chicago pediatric chronic care facility developed an illness that fit the definition for ADV. Eleven children were confirmed to be positive for ADV-7. Eight children died during this outbreak, of which five were considered to be potentially associated with ADV (Gerber 2001).

The applicant notes that it would be impossible to conduct clinical studies in a pediatric population due to the requirement that the enteric coated vaccine tablet must be swallowed intact, without chewing the tablet. They note that, if the tablet were chewed, the live virus could be released into the mouth and respiratory tract and cause a potential respiratory infection.

Medical reviewer comment: The medical reviewer supports the applicant's request for a full pediatric waiver for this product. The basis for this support is based on the following section of the Pediatric Research Equity Act of 2007:

- ***Section 505B(a)(4)(A)(iii): The drug or biological product:***
 - ***(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and***
 - ***(II) is not likely to be used in a substantial number of pediatric patients***

For infants and children below one year of age, the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral would be contraindicated due to safety concerns. The ADV-7 component included in the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is not safe for use in infants and younger children as it is a live vaccine, and would pose a risk to the vaccine recipient of causing an active case of respiratory infection if the contents of the oral vaccine were released in the oral cavity and aspirated. Infants also would run the risk of overt ADV-7 dissemination from this vaccine. In light of this safety concern, the proposed label for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral carries this warning: "Vaccinees and individuals who come into close contact with vaccinees may be exposed to the viruses shed in stool for up to 28 days...Vaccinees should avoid close contact with children less than seven years of age, immunocompromised individuals, and pregnant women during the 28 days following vaccination."

While no existing therapy exists for diseases associated with infection by ADV-4 and ADV-7, administration of the ADV 4/7 Vaccine likely would not result in the prevention of a substantial proportion of these diseases, given the various adenovirus serotypes, in addition to ADV-4 and ADV-7, associated with these syndromes. Moreover, the ADV 4/7 Vaccine would not be likely to be used in a substantial number of pediatric patients, given the safety concerns to children < seven years of age, immunocompromised individuals, and pregnant women associated with the shedding of the vaccine strain viruses in stool for up to 28 days after receiving the vaccine.

Additionally, it is worth noting that the product being licensed involves a combination of two separate vaccines—a tablet containing live ADV-4 and a tablet containing live ADV-7, to be taken concomitantly. As ADV-4 is not an important cause of disease in infants or children, the focus of possible use in the pediatric population is on the ADV-7 component of the product. Use of the ADV-7 component, alone, in any age group, has not been assessed under the development plan for this combination vaccine product, and likely would not be supportable through a supplement to this BLA. Instead, an entirely new development plan for a single ADV-7 vaccine likely would be required.

9.3.2 Pregnancy

Teva Women's Health, Inc. is requesting a waiver of the pregnancy labeling regulations as no pregnancy category fits the teratogenicity criteria as specified in 21 CFR 201.57(c)(9)(i)(A), and a risk benefit assessment does not support the use of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in pregnant women. The requested pregnancy category will be as follows: Pregnancy Category: Contraindicated.

Medical reviewer comment: The medical reviewer supports the designation of the ADV 4/7 Vaccine as pregnancy category CONTRAINDICATED for the following reasons:

- 1. None of the pregnancy categories set forth in 21 CFR 201.57(c)(9)(i)(A) precisely describe the available information regarding the potential for teratogenic effects following the administration of the ADV 4/7 Vaccine to pregnant women. This is because no validated biologically relevant animal model has been developed for evaluating the possible teratogenic effects of the ADV 4/7 Vaccine. Accordingly, the focus of the evaluation of possible teratogenicity must be on available data in humans.*
- 2. No adequate and well controlled studies of the possible teratogenic effects of this product have been conducted in pregnant women. Given the intended use of this vaccine for military populations, and in light of information in the literature documenting fetal harm due to in-utero adenovirus infections of unspecified type, a risk/benefit assessment does not support the use of the ADV 4/7 Vaccine in pregnant women. Therefore Pregnancy Category C is not appropriate.*

3. *No positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience with this product, or studies in humans following administration of this product, has been demonstrated. Accordingly, a Pregnancy Category D designation would not be appropriate.*
4. *Additionally, no studies in animals or humans with this product have been conducted which demonstrated fetal abnormalities or a positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience. Accordingly, a Pregnancy Category X designation would not be appropriate.*
5. *A literature search has provided evidence that intrauterine infection with adenoviruses has been associated with the development of intrauterine abnormalities including fetal hydrops, intrauterine growth restriction, and, in one case report, stillbirth. Neural tube defects also have been associated with intrauterine infection with adenoviruses. None of the reports, however, specified the type of adenovirus that was associated with the intrauterine fetal abnormalities.*
6. *A total of five pregnancies (four in the vaccine group and one in the placebo group) were reported during the Phase 3 study. Among the pregnancies in the vaccine group, three subjects were estimated to have conceived two to thirteen days prior to vaccination. One subject (Subject 11580) conceived approximately twenty-one weeks after she was vaccinated. All four pregnant subjects assigned to the vaccines arm delivered healthy infants at estimated gestational ages between 36 4/7 and 39 5/7 weeks.*
7. *In all pregnancy categories, the regulations call for a balancing of the risk against the likelihood of potential benefit from a vaccine before administration of the product to a pregnant woman. The ADV 4/7 Vaccine is indicated to prevent the development of febrile ARD in the military population, with the vast majority of the vaccine targeted at military recruits. Pregnant women are not eligible for recruitment into the U.S. military. Under these circumstances, in the opinion of this reviewer, there is no benefit that may accrue to a pregnant woman from the use of this vaccine that outweighs even an indirect, theoretical fetal risk. In light of this, even the smallest possibility of fetal risk, defined not from direct studies of this product but pertaining to the evidence from epidemiologic studies and case reports in the literature of fetal harm that unspecified adenovirus types may cause the fetus, is sufficient to recommend against the use of the ADV 4/7 Vaccine in pregnant women. Therefore, the designation of Pregnancy Category: CONTRAINDICATED is most appropriate.*

10. Conclusions—Overall

The available safety, clinical and immunogenicity data support the approval of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral administered as a single dose in military populations in which epidemic respiratory disease due to adenovirus type 4 and type 7 have been shown likely to occur, for prevention of febrile acute respiratory disease due to adenovirus type 4 and adenovirus type 7.

11. Recommendations

11.1 Approval Recommendation

Medical reviewer recommendation: I recommend the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral for approval for a single dose in military populations for active immunization against adenovirus type 4 and type 7, to prevent febrile acute respiratory disease due to these adenovirus serotypes.

11.2 Recommendation on Postmarketing Actions

Because vaccinated military recruits remain in the military setting without close civilian contact for at least 6 weeks, well beyond the 28 day period of viral shedding, the greatest health risk associated with viral shedding and transmission would occur when a recruit is discharged from the military within the 28 day shedding period following vaccination and then comes in close contact with civilians at risk for severe ARD. The applicant proposes to minimize this risk by educating vaccine recipients about the live nature of the vaccine, viral shedding in the stool, the importance of personal hygiene, and avoiding close contact with vulnerable individuals, such as infants and young children, immunocompromised individuals, and pregnant women in the civilian population if discharged early from basic training.

The applicant has proposed enhanced passive surveillance of possible safety signals not identified pre-licensure, utilizing the Defense Medical Surveillance System (DMSS) of the Department of Defense.

The applicant has proposed to utilize the Naval Health Research Center (NHRC) febrile respiratory illness (FRI) program, an active, laboratory-based surveillance of U.S. military populations to study respiratory disease, including FRI and pneumonia among military personnel. The applicant plans to review the NHRC weekly FRI surveillance reports on an annual basis to detect trends in the incidence of FRI due to vaccine strains ADV-4 and ADV-7. This review is intended to provide a means of identifying a potential signal for the transmission of these viruses to the respiratory tract. If the applicant or the NHRC interprets the trend as being related to vaccine safety, CBER will be contacted, with the intention of determining what actions may be needed to assess and mitigate the risk.

The applicant has committed to implement a prospective, observational, exposure-registration and follow-up study of pregnant women exposed to the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral. The purpose of the registry will be to collect data related to birth defects and pregnancy outcomes in the offspring of women inadvertently exposed to the ADV 4/7 Vaccine during pregnancy. The population eligible for enrollment include women in basic training who may have been administered the ADV 4/7 Vaccine during pregnancy or up to six weeks before conception despite the contraindication against use in pregnancy and efforts to prevent vaccination of pregnant women with the ADV 4/7 Vaccine.

The applicant proposes a plan to mitigate the risk of pregnancy in a vaccine recipient which will include: 1) pregnancy testing prior to the administration of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral; 2) product labeling and patient education to inform female recruits that the AD 4/7 Vaccine should be avoided if pregnancy is suspected. The applicant proposes Pregnancy Category: Contraindicated in the label.

11.3 Recommendations on Request for Full Waiver of Pediatric Studies

The medical reviewer supports the applicant's request for a full waiver of studies of the Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in populations ≤ 16 years of age (See Section 9.3). A meeting with the FDA Pediatric Review Committee (PeRC) was held on 06 May 2009. At this meeting, the PeRC concurred with the applicant's request for a full waiver of studies of this product in the pediatric population.

12. Labeling

The package insert submitted by the applicant was in the format required by the FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. The vaccine indication provided in the Indications and Usage section of the Package Insert states the following: Adenovirus Type 4 and Type 7 Vaccine, Live, Oral is a vaccine indicated for active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus Type 4 and Type 7 in military populations 17 through 50 years of age. This indication is supported by the information presented in Section 8.1.2.2, Primary Efficacy Endpoints and Section 8.1.2.5 Safety Outcomes.