

4. FUMISI Clinical Program

4. FLUMIST CLINICAL PROGRAM

A list of 25 clinical trials of FluMist is presented in Table 1. The study number, study design, participant population, study groups, number enrolled, dose regimen, study objectives, and study status are presented within the table.

Pivotal studies to support licensure include:

- Study AV006 and Study AV011 – efficacy and effectiveness of FluMist in children.
- Study AV003 and Study AV009 – efficacy and effectiveness of FluMist in adults.
- Study AV007 and Study AV014 – clinical consistency and bridging to the commercial manufacturing facility.

Safety has been evaluated in all studies including:

- Study AV012 and Study AV019 – large Health Maintenance Organization-based trials in healthy children.

In trials conducted with FluMist, 11 monovalent strains comprising seven trivalent formulations have been administered. In placebo controlled trials, the placebo administered was egg allantoic fluid which was indistinguishable in taste and smell from vaccine.

**Table 1
(1 of 6)
Overview of Clinical Studies with FluMist**

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
AV001	Phase 1 Randomized, Double-Blind, Placebo- Controlled	Healthy Adults, 18-65 years of age	FluMist Placebo	181 58	1 Dose	1. Safety and immunogenicity 2. Spray versus Drops	Completed
AV002	Phase 1/2 Randomized, Double-Blind, Placebo- Controlled	Healthy Children, 18-71 months of age	FluMist Placebo	155 83	1 Dose	1. Safety and immunogenicity 2. Dose response 3. Spray versus drops	Completed
AV002-2	Phase 2 Randomized, Double-Blind, Placebo- Controlled	Healthy Children, 18-71 months of age	FluMist Placebo	79 39	1 Dose	1. Safety and immunogenicity 2. Dose response	Completed
AV003	Phase 3 Randomized, Double-Blind, Placebo- Controlled	Adults 18-41 years of age serosusceptible to at least one influenza strain	FluMist + IM placebo Spray placebo and TIV (IM) Placebo (Spray and IM)	36 33 34	1 Dose	1. Protection against laboratory-documented influenza 2. Safety and immunogenicity	Completed
AV004	Phase 2 Open Label, Randomized, Placebo- Controlled	Healthy Adults, 18-65 years of age	FluMist Placebo spray	15 5	1 Dose	1. Safety of 1995-1996 strains in healthy adults prior to escalating to a 10 ⁷ dose in Study AV002	Completed

**Table 1
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Overview of Clinical Studies with FluMist**

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
AV005	Phase 2 Randomized, Double-Blind, Placebo- Controlled	Healthy Adults, 18-45 years of age	FluMist	16	2 Doses	1. Safety of two doses at 10 ⁷ TCID ₅₀ of 1996-1997 strains in adults	Completed
			Placebo	16			
AV006	Phase 3 Randomized, Double-Blind, Placebo Controlled	Healthy Children, 15-71 months of age	FluMist	<u>Year One</u> 1070	<u>Year One</u> 1 or 2 Doses	1. Efficacy of FluMist to prevent culture- confirmed influenza	Completed
			Placebo	532	<u>Year Two</u> 1 Dose		
			FluMist	917			
			Placebo	441			
AV007	Phase 3 Randomized, Double-Blind, Placebo- Controlled	Healthy Children, 12-36 months of age	FluMist	400	2 Doses	1. Lot consistency (3 lots) 2. Bridging to vaccine used in efficacy Study AV006	Completed
			Placebo	100			
AV008	Phase 3 Randomized, Double-Blind, Placebo- Controlled	Adults ≥65 Years, ≥1 Other high-risk factor	FluMist + TIV	100	1 Dose	1. Safety of co- administration of FluMist with TIV in high-risk adults	Completed
			Placebo + TIV	100			
AV009	Phase 3 Randomized, Double-Blind, Placebo- Controlled	Healthy working adults, 18-64 years of age	FluMist	3041	1 Dose	1. Safety 2. Effectiveness in reducing influenza- like illness, absenteeism, health care utilization	Completed
			Placebo	1520			

Table 1
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Overview of Clinical Studies with FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
AV010	Phase 3 Randomized, Double-Blind, Placebo- Controlled	Children with moderate to severe asthma, 9-17 years of age	FluMist Placebo	24 24	1 Dose	1. Safety of FluMist in children with moderate to severe asthma	Completed
AV011	Phase 3 Randomized, Vaccine Challenge	Healthy children from Study AV006	Prior FluMist Prior Placebo	144 78	1 Dose	1. Efficacy of FluMist to prevent shedding of vaccine virus (H1N1)	Completed
AV012	Phase 3 Open Label, Unvaccinated control communities	Healthy children 18 months - 18 years of age conducted at Scott & White HMO, Temple, Texas	FluMist	<u>Year One</u> 4298 <u>Year Two</u> 5251 <u>Year Three</u> 5150	1 Dose	1. Safety and herd immunity for control of epidemic influenza	<u>Year One</u> Completed <u>Year Two</u> Completed <u>Year Three</u> Enrolment and Follow-up Completed; Analysis Ongoing
AV014	Phase 3 Randomized Double-Blind	Healthy children 12-42 months of age	FluMist	225	2 Doses	1. Comparison of safety, tolerability and immunogenicity of FluMist from two manufacturing facilities	Completed
AV015	Phase 3 Open Label	Healthy children who participated in AV006 approximately 3-8 years of age at time of re- enrollment	FluMist	949	1 Dose 2 Doses	1. Safety and tolerability for third year of vaccination. 2. Safety and tolerability of primary vaccination with FluMist in prior placebo recipients	Completed

Table 1
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Overview of Clinical Studies with FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
AV017	Phase 3 Open Label (old cohort) and Randomized Double-Blind Placebo- Controlled (new cohort)	Healthy AV006 participants and their siblings	FluMist	1028	1 or 2 Doses	1. Safety, tolerability and immunogenicity for fourth year of vaccination. 2. Safety, tolerability and immunogenicity of primary vaccination with FluMist in prior placebo recipients and new cohort	Completed
		New similar age cohort	FluMist	147	2 Doses		
			Placebo	70			
AR001	Phase 3 Randomized, Double-Blind	Adults and children	FluMist rFluMist ^a	224 225	1 Dose if ≥9 years, 2 Doses if 1-8 years	1. Comparison of classical FluMist versus recombinant FluMist (rFluMist)	Completed
DMID #98-005 (NIH)	Phase 2 Randomized, Double-Blind, Placebo- Controlled	Adults 18-50 years of age	HIV-infected FluMist	28	1 Dose	1. Safety, vaccine virus shedding and immunogenicity in HIV-infected adults 2. Effects on HIV RNA and CD4 counts	Completed
			Placebo	29			
DMID #99-012 (NIH)	Phase 2 Randomized, Double-Blind, Placebo- Controlled Cross-Over Design	Children 1-7 years of age	HIV-infected FluMist	23	1 Dose of placebo and 2 doses of FluMist	1. Safety, vaccine virus shedding and immunogenicity in HIV-infected children 2. Effects on HIV RNA and CD4 counts	Completed
			Placebo	24			
			HIV-negative FluMist	25			
			Placebo	25			

^a rFluMist = FluMist produced by recombinant methods; only one strain of rFluMist, A/Shenzhen/227/95 (H1N1), was made using recombinant methodology.

**Table 1
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Overview of Clinical Studies with FluMist**

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
Veterans Affairs (VA) CSP #448	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Adults ≥50 years of age with COPD	FluMist + TIV Placebo + TIV	1107 1108	1 Dose	1. Safety and efficacy between vaccination regimens in adults ≥50 years of age with COPD	Enrollment and Follow-up Completed; Analysis ongoing
D145-P500 Wyeth-Lederle Vaccines, Non-IND	Randomized, Double-Blind, Placebo-Controlled	Healthy children 8–36 months of age attending day care in Finland	FluMist Placebo	98 99	1 or 2 [2 nd dose optional, open label]	1. Safety 2. Transmissibility	Completed
D153-P500 Wyeth-Lederle Vaccines Non-IND	Randomized, Double-Blind	Healthy children 12 to 36 months of age in South Africa	FluMist ^a	697	2 Doses	1. Safety 2. Immunogenicity	Completed
AL002	Randomized, Single Blind and Open-Label for Children <9	Adults and children	FluMist	314	1 Dose ≥9 years 2 Doses 1–8 years	1. Safety 2. Immunogenicity	Completed
AV018	Randomized, Double-Blind, Placebo-Controlled	Healthy children, 12 to 15 months of age	MMRII [®] / VARIVAX [®] with FluMist or Placebo or FluMist alone	Planned 1200	2 Doses	1. Safety and Immunogenicity with concurrent vaccinees	Ongoing

^a Participants randomized to FluMist or investigational liquid formulation. Only FluMist recipients discussed herein.

Table 1
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Overview of Clinical Studies with FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives	Study Status
AV019	Randomized, Double-Blind, Placebo-Controlled	Healthy children 1-17 years of age Conducted at Kaiser Permanente HMO, Northern California	FluMist	9689 evaluable <u>6473</u> 3769 (1-8 years of age) 2704 (9-17 years of age)	2 doses (1-8 years of age) 1 dose (9-17 years of age)	1. Safety	Enrollment and Follow-up Completed; Analysis Ongoing
			Placebo	<u>3216</u> 1868 (1-8 years of age) 1348 (9-17 years of age)			