A Phase II Randomized, Observer-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Immunogenicity and Safety of Multiple Formulations of an RSV F Nanoparticle Vaccine with Aluminum, in Healthy Women of Child-Bearing Age

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ABSTRACT

Background: The RSV F nanoparticle vaccine (RSV F vaccine) is a near-full length recombinant F protein that is being evaluated for use in maternal immunization to prevent infant RSV disease. In this study, various dose schedules, antigen and aluminum phosphate (Al) doses were evaluated for safety and immunogenicity in women of childbearing age in preparation for use in pregnant women.

Methods: In a randomized, observer-blind, placebo-controlled trial, 720 non-pregnant 18 to 35 year-old women were immunized with either 60µg of RSV F vaccine on days 0 and 28, or 120µg of the RSV F vaccine administered once. A range of Al (0.2, 0.4 and 0.8mg) doses were used. Controls included 60µg RSV F vaccine/1.2mg Al given once or 60µg RSV F vaccine/0.80mg Al given twice, modelling earlier clinical trial regimens; and placebo. Primary endpoints included safety over 180 days and anti-F IgG response, evaluated at multiple time points through day 91 and compared to the 60µg F vaccine/0.8mg Al dosage given twice. Palivizumab-competitive antibodies (PCA) and RSV/A and B microneutralization titers (MN) were also evaluated.

Results: The vaccine was well tolerated with no vaccine-related SAEs. Mild to moderate local reactogenicity was more frequent in vaccinees, but not related to dose of Al or RSV F vaccine antigen. The immune response to 120µg RSV F/0.4mg Al administered once was non-inferior to 60µg antigen/0.8mg Al given twice when compared at day 56, and superior at days 14 and 28; the area under the curve of anti-F IgG level was greatest for this regimen over at least the first 49 days after treatment. PCA levels peaked at 396µg/mL two weeks after the 120µg RSV F/0.4mg Al administration and were sustained above 300µg/ml over the first 56 days post-immunization. RSV A and B MNs rose significantly in all groups, with the greatest increases seen in the subjects with the lowest baseline titers.

Conclusions: The vaccine was well tolerated. The 120µg RSV F/0.4mg Al regimen provides a one dose option that induces high levels of antibodies including anti-F IgG, PCA and RSV/A and B MN activity with a time course suitable for third trimester maternal immunization.

TRIAL OBJECTIVES

Prior data had demonstrated improved immunogenicity of the RSV F vaccine with aluminum, and with two-dose regimens at 60-90µg of RSV F antigen. Because of the significant convenience and compliance premium of a one-dose regimen, and the desire to minnmize aluminum, in maternal immunization, the trial was undertaken:

- To evaluate the immunogenicity and antibody kinetics associated with two-dose regimens using 60µg doses of the RSV F protein vaccine adsorbed to 0.8, 0.4, or 0.2mg aluminum (as $AlPO_4$);
- To evaluate the immunogenicity and antibody kinetics associated with one-dose regimens using 120µg doses of the RSV F protein vaccine adsorbed to 0.8, 0.4, or 0.2mg aluminum (as $AlPO_4$); and
- To describe the safety of the above regimens.

METHODS

- 720 healthy women 18 to 35 y.o. enrolled in a randomized, observer-blinded, placebo-controlled trial.
- Each subject received two IM injections, on Days 0 and 28.

Group	N	RSV F dose (µg)	Al dose (mg)	Day 0	Day 28
A	90	60	1.2	active	placebo
B	90	60	0.8	active	active
C	90	60	0.4	active	active
D	90	60	0.2	active	active
E	90	120	0.8	active	placebo
F	90	120	0.4	active	placebo
G	90	120	0.2	active	placebo
H	90	0	0	placebo	placebo

- All subjects provided immunogenicity data on days 0, 14, 28, ,56, and 91; subcohorts bled weekly in intervals.
- Six (6) month safety follow-up.

SUBJECT DEMOGRAPHY and DISPOSITON

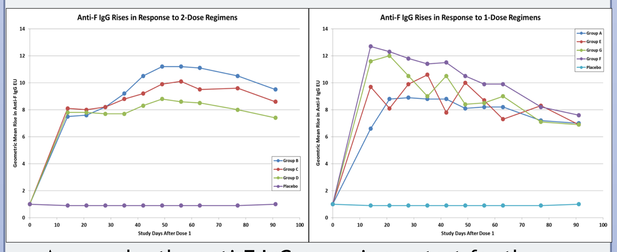
- Mean age 27.2 years,
- Approximately 40% < 26 years, 60% 26 to 35 years,
- 67-77% Caucasian,
- 15-27% African American,
- 4-10% other racial groups,
- 13-27% Hispanic,
- Approximately one-third have children under 5 years in the household,
- 92% completed day 91,
- No discontinuations due to AE.

SAFETY

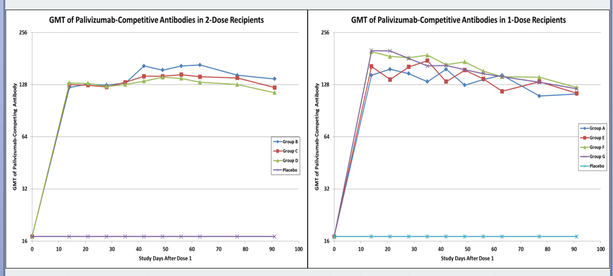
Group	A	B	C	D	E	F	G	H
RSV F (µg)	60	60	60	60	120	120	120	0
Al (µg)	1200	800	400	200	800	400	200	0
Active dose days	0	0, 28	0, 28	0, 28	0	0	0	None
Safety N	89	91	89	92	93	89	90	87
Subjects (%):								
Any TEAE	80 (90)	83 (91)	80 (90)	76 (83)	83 (89)	72 (81)	81 (90)	62 (71)
Solicited AE	74 (83)	77 (85)	73 (82)	68 (74)	75 (81)	68 (76)	72 (80)	43 (49)
Severe	4 (5)	6 (7)	5 (6)	5 (5)	5 (5)	4 (5)	3 (3)	3 (3)
Local	65 (73)	69 (76)	64 (72)	56 (61)	69 (74)	61 (69)	66 (73)	16 (18)
Systemic	48 (54)	58 (64)	53 (60)	52 (57)	53 (57)	52 (58)	54 (60)	41 (47)
Unsolicited AE	62 (70)	62 (68)	51 (57)	55 (60)	65 (70)	44 (49)	47 (52)	51 (59)
Severe	5 (6)	6 (7)	5 (6)	2 (2)	4 (4)	3 (3)	0	5 (6)
Related	12 (14)	15 (17)	11 (12)	14 (15)	16 (17)	9 (10)	6 (7)	10 (12)
Severe & related	0	0	0	0	1 (1)	1 (1)	0	0
Medical visit	11 (12)	14 (15)	13 (15)	15 (16)	13 (14)	8 (9)	13 (14)	13 (15)
Serious AE	0	2 (2)	1 (1)	0	3 (3)	1 (1)	0	2 (2)

- Little dose-related trend in solicited AEs with RSV F or aluminum dose.
- No clear trends in severe, related, or serious AEs.

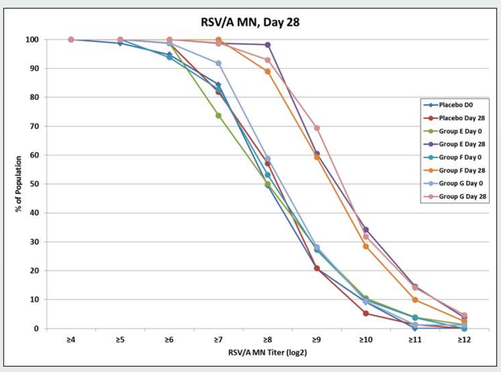
IMMUNE RESPONSES



- Area under the anti-F IgG curve is greatest for the group receiving the single 120µg RSV F dose with 0.4mg Al as late as Day 49, and is <20% inferior as late as Day 56.



- Palivizumab-competitive antibodies show similar pattern.
- Peak levels in one-dose groups suggest 360-400µg/mL of palivizumab-like activity.



- Titers of RSV/A microneutralizing (MN) antibodies show a strong and uniform shift upward in single-dose recipients.
- RSV/B microneutralization pattern similar.

SUMMARY and CONCLUSIONS

- All formulations of RSV F with aluminum had similar safety profiles.
- A single-dose regimen providing 120µg RSV F adsorbed to 0.4mg of Al provided the greatest area under the anti-F IgG response curve through at least 49 days.
- Peak antibody responses are attained at 14 days, providing a flexible regimen for dosing in the third trimester.
- Palivizumab-competitive antibody levels and neutralizing responses are consistent with anti-F IgG data.