

**Toxicology Review of Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine
(Final Report)**

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File: BLA 125768, original submission

Product: Respiratory Syncytial Virus Bivalent Stabilized Prefusion F Subunit Vaccine

Reviewer: Nabil Al-Humadi
BLA sections reviewed:
4.2.3.2 Repeated dose toxicity studies
4.2.3.5 Reproductive and developmental toxicity studies

Type and date of submission: Original, September 30th,2022

Sponsor: Pfizer Inc., 235 East 42nd Street, NY 10017

Proposed indication: Prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infant from birth through 6 months of age by active immunization of pregnant individuals.

Proprietary name: ABRYSVO

Cross references: DMF (b) (4), DMF (b) (4), (b) (4), STN (b) (4)

Division name: OVRR/DVRPA

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Précis:

Study number 1:

In this repeat (study days [SD's] 1, 22, and 36) dose toxicology study, rats were assigned to 4 different groups and treated with control or test article. Animals, 15 per sex per group, were treated intramuscularly (IM) with a final injection volume of 500 µL (250 X 2) per dosing day. The human dose was used in this study. Immunological responses were reported.

Study number 2 (Developmental toxicology study):

In this repeat (study days M-21, M- 7 [before the start of mating phase] and on gestation days G10 and G24) dose reproductive toxicology study, rabbits were assigned to 4 different groups and treated with control or test article). Animals, 22 per subgroup, were treated intramuscularly (IM) with a final injection volume of 500 µL per dosing day. The human dose was used in this study. Immunological responses were reported.

Introduction:

RSV is a major cause of respiratory infection in both infants and older adults. RSV infection follows a seasonal pattern causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall (1). RSV has 2 subgroups, A and B (either can cause severe disease), which co-circulate.

In infants, less than 1 year of age, respiratory syncytial virus (RSV) is the leading cause of hospitalization. Globally, RSV causes more than 34 million new acute respiratory illness and up to 200,000 deaths each year (2). In immunosuppressed children, immunosuppressed adults, and elderly, RSV causes severe respiratory illness (3-5).

Two indications are proposed to protect against RSV disease:

- 1- Prevention of RSV-associated lower respiratory tract disease in infants by active immunization of pregnant women.
- 2- Prevention of RSV-associated moderate to severe lower respiratory tract disease in adults 60 years of age and older by active immunization.

Pfizer's investigational RSV vaccine contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. The stabilized prefusion F glycoproteins in the bivalent vaccine are composed of engineered F glycoprotein ectodomains (one from the subgroup A Ontario genotype and one from the subgroup B Buenos Aires genotype, representing wild-type contemporary strains), (b) (4)

(b) (4). The vaccine is prepared for injection by reconstituting the lyophilized drug product with (b) (4) : sterile water for injection (b) (4). The lyophilized vaccine contains excipients that, after reconstitution, will have the following concentrations: (b) (4) Tris, (b) (4) sucrose, (b) (4) sodium chloride, and (b) (4) polysorbate 80.

The pre-IND meeting did not include a toxicology representative (dated June 7, 2017).

Proposed clinical study:

The clinical study is a phase 1/2 randomized, placebo-controlled, observer-blind, dose-finding first in human (FIH) study. The study will evaluate the safety, tolerability, and immunogenicity of up to 6 different RSV vaccine candidates with bivalent formulations (RSV A and B) at 3 escalating dose levels of 60 µg (30 µg A and 30 µg B), 120 µg (60 µg A and 60 µg B), and 240 µg (120 µg A and 120 µg B) of the prefusion RSV F antigen, with or without Al(OH)₃, when administered alone or concomitantly with SIIV.

A sentinel cohort (phase 1) and an expanded cohort (phase 2) for each dose level in each age group (see figure below) will be included in this study. The age groups will run in parallel but independently from each other.

Subjects will be enrolled into 2 age groups in the sentinel cohort (phase 1) study:

1- Male and female subjects 18 to 49 years of age.

2- Male and female subjects 50 to 85 years of age.

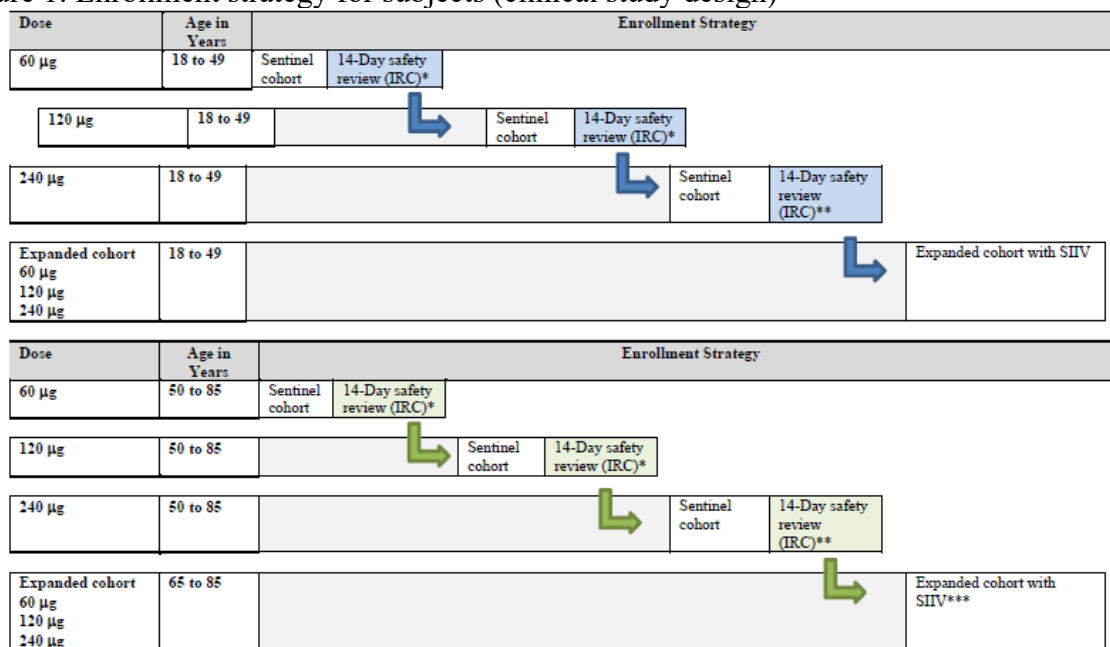
Subjects will be enrolled into 2 age groups in the expanded cohort (phase 2) study:

1- Male and female subjects 18 to 49 years of age.

2- Male and female subjects 65 to 85 years of age.

A single dose of RSV vaccine will be given to sentinel-cohort subjects to assess 3 escalating dose levels of the RSV vaccine candidate with or without Al(OH)₃.

Figure 1: Enrollment strategy for subjects (clinical study design)



*14-Day safety review by internal review committee (IRC). If the safety data in the sentinel cohort in a given age group are acceptable, the IRC will recommend proceeding with randomization of the sentinel cohort at the next dose level for the specified age group.

**14-Day safety review by internal review committee (IRC). If the safety data in the sentinel cohort 240-µg dose level are acceptable, the IRC will recommend proceeding with randomization of additional subjects to the expanded cohort at all 3 dose levels.

***Commercially available seasonal inactivated influenza vaccine (SIIV) or SIIV high-dose (HD) will be used for subjects 65 to 85 years of age. Study sites will be provided with details of which commercially available SIIV or SIIV HD will be provided prior to the start of enrollment of the expanded cohort.

Studies reviewed for this BLA:

General toxicology studies

- 1- 38-Day Intramuscular Toxicity Study of PF-07052944 in (b) (4) Rats with A 1-Month Recovery. Study number: 17GR075

Reproductive Studies

- 2- Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of RSV Bivalent Vaccine Formulations by Intramuscular Administration in the Rabbit. Study Number: AB22373

Studies not reviewed in all amendments:

None.

Toxicology Study Reviews:

Study number 1:

Title and study number: 38-Day Intramuscular Toxicity Study of PF-07052944 in (b) (4) Rats with A 1-Month Recovery. Study number: 17GR075

Performing laboratory: (b) (4)

Study initiation date: June 09, 2017

Final report date: August 30, 2017

Test article batch/lot:

<u>Test article</u>	<u>Lot No.</u>	<u>Expiration Date</u>	<u>Purity %</u>
PF-07052944	00709594-0313	05/09/2018	NR
PF-07013205-0.4 mg/mL (adjuvant)	00709594-0295-A1	03/09/2018	NR
PF-07048679	00709594-0312	05/02/2018	NR
0.9% Sodium Chloride	J6H055	12/31/2018	NR

NR = Not reported.

Animal species and strain: (b) (4) rats

Breeder/supplier: (b) (4)

Number of animal per group and sex: 120 (15/sex/group).

Age: 10 weeks old

Body weight range: 261.8-311.3 grams for males and 188.0-228.4 grams for females

Route and site of administration: Intramuscular (IM)

Volume of injection: The dose volume was 500 μ L (0.25 mL in left and right quadriceps) per animal.

Frequency of administration and study duration: Animals were dosed on study days 1, 22, and 36. Study duration was 66 days.

Dose: 240 μ g/day.

Stability: Analysis of stability, homogeneity and concentration of the test article under test conditions was not performed as part of the study. Stability studies were performed by the sponsor of the IND.

Based on the stability testing, PF-07052944 and PF-07048679 formulations are stable for (b) (4) hours at room temperature. Expiration dates of the test article are provided above.

Storage and handling of PF-07052944 Lyo RSV bivalent drug product: 2 months at (b) (4).

Storage and handling of PF-07048679 Lyo RSV formulation matrix: 2 months at (b) (4).

Storage and handling of PF-07013205 alhydrogel adjuvant product for RSV: 1 month at (b) (4).

Means of administration: Intramuscular (IM)

Report status: Final

Experimental design:

Animals were randomized and assigned to 4 different groups. Each group consisted of 15 animals/sex/group. Animals were dosed by intramuscular route on study days 1, 22, and 36. The details of the study design are listed in the following table:

Experimental Design					
Group Number	PF-07052944 or Vehicle Dose/Dose Day ($\mu\text{g}/\text{Day}$)	Number of injections/Dose Day	Dose Volume (mL/injection site)	Animal Numbers ^{e,f}	
				Males	Females
1	0 ^a	2	0.25	1-15	61-75
2	0 ^b	2	0.25	16-30	76-90
3	240 ^c	2	0.25	31-45	91-105
4	240 ^d	2	0.25	46-60	106-120

a. Sterile Saline

b. Vehicle 2 (PF-07013205 + PF-07048679; $\text{Al}[\text{OH}]_3$ control)

c. 120 μg (b) (4) + 120 μg (b) (4)/dose day; reconstituted with sterile water for injection

d. 120 μg (b) (4) + 120 μg (b) (4)/dose day; reconstituted with PF-07013205 ($\text{Al}[\text{OH}]_3$)

e. The first 10 animals/sex/group, by ascending animal order, were designated for necropsy at the end of the dosing phase.

f. The remaining animals were retained for a 1-month recovery phase after the last dose administration.

Table 1: Experimental design (study # 1); sponsor provided

Methods:

Randomization procedure: Yes.

Statistical analysis plan: Yes.

The following parameters were evaluated: Cage side observations (twice daily), dose site observations (predose on dosing phase days 1, 22, and 36 and at approximately 4 and 24 hours postdose on all animals), body weights (dosing days; 1, 22, and 36, non-dosing days on; 4, 8, 15, 25, and 29, and for recovery phase on days; 1, 8, 15, 22, and 27/26 [males/females]), body temperature (predose on dosing phase days 1, 22, and 36 and at approximately 4 and 24 hours postdose (HPD) from all animals), food consumption (dosing days 4, 8, 15, 22, 25, 29, and 36 and for recovery phase on days 8, 15, 22 and 26), ophthalmoscopy (week 5 (day 32/31 [males/females])), clinical chemistry, hematology, coagulation, biomarkers [α -2-macroglobulin and creatine kinase], urinalysis (see table below), and serology (prior to initiation of dosing (PID, day 11), prior to dosing on day 36, day 38 of the dosing phase, and on recovery phase days 8/7 (males/females) and 28/27 (males/females)). Gross anatomy at termination and organ weights and histopathology were evaluated/determined on selected tissues.

Schedule for Collection of Samples for Clinical Laboratory Measurements					
		Dosing Phase			Recovery Phase
Parameter	Day of Study	3	22	38 ^c	28/27 (males/females) ^{c, d}
Hematology		X ^a	NA	X	X
Coagulation		NA	NA	X	X
Clinical Chemistry (Core Chemistry)		X ^b	NA	X	X
Clinical Chemistry (Other Biomarkers)/Serum		X ^b	X	X	X
Urinalysis		NA	NA	X	X

a. First 7 animals/sex/group.

b. Last 8 animals/sex/group.

c. Evaluated on animals scheduled for necropsy (males/females).

d. Recovery Phase Day 28/27 (males/females) = Day 66/65 (males/females) in the appendices.

X = Sample Collected

NA=Not applicable

Site of blood collection was not specified.

Table 2: Schedule for collection of samples for clinical laboratory measurements (study # 1); sponsor provided

Parameters	Frequency of Testing
Cageside observation ¹	Twice daily
Dose site observations	Predose on dosing phase days 1, 22, and 36 and at approximately 4 and 24 hours postdose on all animals
Body weight	Dosing days; 1, 22, and 36, non-dosing days on; 4, 8, 15, 25, and 29, and for recovery phase on; days 1, 8, 15, 22, and 27/26 (males/females)
Food consumption	Dosing days 4, 8, 15, 22, 25, 29, and 36 and for recovery phase on days 8, 15, 22 and 26
Body temperature	Predose on dosing phase days 1, 22, and 36 and at approximately 4 and 24 hours postdose (HPD) from all animals
Ophthalmologic exam	Week 5 (day 32/31 [males/females])
Serology	Prior to initiation of dosing (PID, day 11), prior to dosing on day 36, day 38 of the dosing phase, and on recovery phase days 8/7 (males/females) and 28/27 (males/females)
Necropsy	Days 38 and 66
Tissues for histopathology	Days 38 and 66

Table 3: Parameters evaluated (study # 1)

Postmortem procedures: The following tissues were collected at necropsy. Those tissues marked with an asterisk were weighed. Tissues examined for histology are marked with an '!'.

Organ/Tissue	Collected	Not collected
Adrenal glands	!*	
Aorta	!	
Bone, sternum	!	
Bone marrow (sternum)	!	

¹ Cageside observations include mortality, morbidity, general health and signs of toxicity.

Organ/Tissue	Collected	Not collected
Bone marrow smear	!	
Brain	!*	
Cecum	!	
Cervix	!	
Colon	!	
Duodenum	!	
Epididymides	!*	
Esophagus	!	
Eyes	!	
Fallopian tubes		X
Gall bladder		X
Gut Associated Lymphoid Tissue (GALT)	!	
Gross lesions	!	
Harderian gland	!	
Heart	!*	
Ileum	!	
Injection site (left and right, muscle and skin)	!	
Jejunum	!	
Joint (left and right)	!	
Kidneys	!*	
Lacrimal gland (extra- and intra-orbital)	!	
Larynx	!	
Liver	!*	
Lungs	!	
Lymph nodes (draining, inguino-femoral, and mesenteric)	!	
Mammary gland	!	
Optic nerve	!	
Ovaries	!*	
Oviduct	!	
Pancreas	!	
Pituitary gland	!	
Prostate	!*	
Rectum		X
Salivary glands	!	
Sciatic nerve	!	
Seminal vesicle	!	
Skeletal muscle	!	
Skin and anexa	!	

Organ/Tissue	Collected	Not collected
Spinal cord	!	
Spleen	!*	
Stomach	!	
Testes	!*	
Thymus	!*	
Thyroid (include parathyroid)	!	
Tongue	!	
Trachea	!	
Ureters	!	
Uterus	!	
Urinary bladder	!	
Vagina	!	
Zymbal's gland		X

Table 4: Histology examination (study # 1)

Tissues identified in the table above were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Results:

No test article-related morbidity and/or mortality were reported.

Clinical Chemistry, hematology, and coagulation:

CLINICAL CHEMISTRY		
MEASUREMENT RELATED TO	END POINTS DIFFERENT THAN THE CONCURRENT CONTROL (LIST THE ENDPOINT STUDY DAY (SD), SEX, DOSE GROUP (G), DIRECTION, FOLD CHANGE if great than 1.5 so indicated otherwise ≤ 1.5)	NOT OF NOTE
ELECTROLYTE BALANCE		Calcium, chloride, potassium, sodium, phosphorus
CARBOHYDRATE METABOLISM		Glucose
LIVER FUNCTION: A) HEPATOCELLULAR		Aspartate aminotransferase (AST or SGOT) Alanine aminotransferase (ALT or SGPT)
B) HEPATOBILIARY		Total bilirubin Alkaline phosphatase (ALP)
ACUTE PHASE REACTANTS		Fibrinogen (see under coagulation) C-reactive protein*
KIDNEY FUNCTION	Urine volume SD38 F $\downarrow \leq 0.5$ G2 SD38 F $\downarrow \leq 0.4$ G3 SD38 F $\downarrow \leq 0.4$ G4 SD27R F $\uparrow \geq 2.6$ G2 SD27R F $\uparrow \geq 1.8$ G3 SD27R F $\uparrow \geq 1.9$ G4	Creatinine Blood Urea Nitrogen

CLINICAL CHEMISTRY		
MEASUREMENT RELATED TO	END POINTS DIFFERENT THAN THE CONCURRENT CONTROL (LIST THE ENDPOINT STUDY DAY (SD), SEX, DOSE GROUP (G), DIRECTION, FOLD CHANGE if great than 1.5 so indicated otherwise ≤ 1.5)	NOT OF NOTE
OTHERS (ACID/BASE BALANCE, CHOLINESTERASES, HORMONES, LIPIDS, METHEMOGLOBIN, AND PROTEINS)	Creatine kinase SD22 M $\downarrow \leq 0.6$ G2 SD27R F $\downarrow \leq 0.6$ G3 Fasting Triglycerides SD28R M $\downarrow \leq 0.5$ G4 A2M SD38 F $\uparrow \geq 2.2$ G4	Albumin (A) Total protein Carbon dioxide Globulin A/G ratio Total Cholesterol GGT Lactate dehydrogenase

R = Recovery. M = Male. F = Female. * Not applicable.

Table 5: Clinical chemistry results (study # 1)

Clinical chemistry results show a decrease in urine volume in groups 2, 3, and 4 females at study day 38. Urine volume was increased in groups 2, 3, and 4 females at study day 27 of recovery.

Creatine kinase levels were decreased in group 2 males at study day 22 and group 3 females at study day 27 of recovery. Triglyceride levels were decreased in group 4 males at study day 28 of recovery. Alpha 2 macroglobulin (A2M) levels were increased in group 4 females at study day 38.

HEMATOLOGY		
MEASUREMENT RELATED TO	END POINTS DIFFERENT THAN THE CONCURRENT CONTROL (LIST THE ENDPOINT, STUDY DAY (SD), SEX, DOSE GROUP (G), DIRECTION, FOLD CHANGE if great or less than 1.52, ie, ≥ 1.6 or ≤ 1.6)	Not of NOTE
red blood cells		Hematocrit (Hct) Hemoglobin Conc. (Hb) Mean Corp. Hb. (MCH) Mean Corp. Hb. Conc. (MCHC), Mean Corp. Volume (MCV) Total Erythrocyte Count (RBC) Reticulocytes
white blood cells	Monocyte count: SD38 F $\uparrow \geq 1.7$ G2 SD38 F $\uparrow \geq 2.3$ G4 SD27R F $\uparrow \geq 1.8$ G4 Neutrophil count SD3 M $\uparrow \geq 1.7$ G4 SD38 M $\uparrow \geq 1.7$ G4	Macrophage Leukocytes Lymphocyte count

² With rounding up at the tenth decimal place. Therefore, 1.54 or less becomes 1.5 and is not reported and 1.55 or greater becomes 1.6 and is reported.

HEMATOLOGY		
MEASUREMENT RELATED TO	END POINTS DIFFERENT THAN THE CONCURRENT CONTROL (LIST THE ENDPOINT, STUDY DAY (SD), SEX, DOSE GROUP (G), DIRECTION, FOLD CHANGE if great or less than 1.52, ie, ≥ 1.6 or ≤ 1.6	Not of NOTE
	SD38 F $\uparrow \geq 2.8$ G4 Eosinophils count SD3 M $\downarrow \leq 0.6$ G3 SD38 F $\uparrow \geq 3.2$ G4 Basophils SD38 M $\uparrow \geq 1.7$ G4 SD28R M $\downarrow \leq 0.3$ G2 SD28R M $\downarrow \leq 0.3$ G3 SD28R M $\downarrow \leq 0.5$ G4 SD3 F $\downarrow \leq 0.4$ G3 SD3 F $\downarrow \leq 0.6$ G4 Large Unstained Cells (LUC) SD28R M $\downarrow \leq 0.6$ G2 SD28R M $\downarrow \leq 0.5$ G3 SD28R M $\downarrow \leq 0.6$ G4 SD3 F $\downarrow \leq 0.6$ G2 SD38 F $\uparrow \geq 2.5$ G4 SD27R F $\uparrow \geq 3.0$ G2 SD27R F $\uparrow \geq 2.0$ G3 SD27R F $\uparrow \geq 5.0$ G4 White Blood Cells (WBC) SD38 F $\uparrow \geq 1.7$ G4	
clotting potential		Mean platelet volume Prothrombin time Activated partial-thromboplastin time clotting time Platelet count Fibrinogen
others		Bone marrow cytology

R = Recovery. M = Male. F = Female.

Table 6: Hematology results (study # 1)

Monocyte levels were increased in groups 2 and 4 females at study day 38. Monocyte levels were increased in group 4 females at study day 27 of recovery. Neutrophil levels were increased in group 4 males at study days 3 and 38. Neutrophil levels were increased in group 4 females at study day 38. Eosinophil levels were decreased in group 3 males at study day 3. Eosinophil levels were increased in group 4 females at study day 38. Basophil levels were increased in group 4 males at study day 38. Basophil levels were decreased in groups 2, 3, and 4 males at study day 28 of recovery. Basophil levels were decreased in groups 3 and 4 females at study day 3. Large unstained cells (LUC) levels were decreased in groups 2, 3, and 4 males at study day 28 of recovery. Large unstained cells (LUC) levels were decreased in group 2 females at study day

3. Large unstained cells (LUC) levels were increased in group 4 females at study day 38. Large unstained cells (LUC) levels were increased in groups 2, 3, and 4 females at study day 27 of recovery. White blood cells (WBC) levels were increased in group 4 females at study day 38.

Systemic toxicity:

No treatment-related, mortality, nor any toxicologically relevant changes in clinical signs, food consumption, body weight, body temperature, injection sites findings, ophthalmoscopic parameters, or gross pathology were reported.

Organ Weight:

SEX		MALES (DOSING PHASE/RECOVERY PHASE)			
GROUPS		1 (CONTROL)	2	3	4
NUMBER OF ANIMALS		10/5	10/5	10/5	10/5
BODY WEIGHT (terminal)		340/382	347/387	334/377	341/373
BRAIN		2.01/2.04	1.97/2.00	1.97/2.02	1.95/1.98
ADRENALS		0.065/0.066	0.064/0.072	0.065/0.058	0.062/0.069
EPIDIDYMIDES		1.48/1.46	1.46/1.54	1.47/1.36	1.33/1.65
HEART		0.98/1.10	1.01/1.07	0.99/1.05	0.97/1.12
KIDNEYS		2.30/2.55	2.37/2.57	2.28/2.51	2.27/2.41
LIVER		8.53/9.73	8.50/9.39	8.21/9.10	8.22/8.93
LUNGS		NC	NC	NC	NC
LYMPH NODES	Right	NC	NC	NC	NC
	Left	NC	NC	NC	NC
SPLEEN		0.635/0.694	0.622/0.641	0.602/0.612	0.635/0.649
TESTES		3.64/3.83	3.87/3.81	3.62/3.54	3.65/3.68
PITUITARY		NC	NC	NC	NC
PROSTATE		1.22/1.13	1.19/1.17	1.08/1.07	1.15/1.24
THYROID and PARATHYROID		NC	NC	NC	NC
THYMUS		0.427/0.366	0.438/0.481	0.379/0.365	0.420/0.367
OVARIES					
UTERUS					

Absolute weights are expressed as mean (grams). Entries in table are expressed both as organ weight from animals taken at the end of the terminal phase and recovery phase of the study (main phase organ weight/recovery phase organ weight).

Table 7: Male's organ weight (study # 1)

Epididymides weight was increased 13% in group 4 males at study day 38. Spleen weight was decreased 12% in group 3 males at study day 28 of recovery. Prostate weight was decrease 11% in group 3 males at study day 38. Thymus weight was decreased 11% in group 3 males at study day 38. Thymus weight was increased 31% in group 2 males at study day 28 of recovery.

SEX		FEMALES (DOSING PHASE/RECOVERY PHASE)			
GROUPS		1 (CONTROL)	2	3	4
NUMBER OF ANIMALS		10/5	10/5	10/5	10/5
BODY WEIGHT (terminal)		203/216	208/213	205/211	203/217
BRAIN		1.82/1.91	1.82/1.79	1.83/1.91	1.83/1.83
ADRENALS		0.079/0.079	0.076/0.075	0.078/0.082	0.086/0.082
EPIDIDYMIDES					
HEART		0.68/0.72	0.68/0.64	0.72/0.68	0.66/0.92
KIDNEYS		1.56/1.57	1.59/1.50	1.51/1.61	1.60/1.49
LIVER		5.12/5.27	5.18/5.09	5.08/5.13	5.22/5.32
LUNGS		NC	NC	NC	NC
LYMPH NODES	Right	NC	NC	NC	NC
	Left	NC	NC	NC	NC
SPLEEN		0.428/0.437	0.497/0.389	0.427/0.437	0.492/0.475
TESTES					
PITUITARY		NC	NC	NC	NC
PROSTATE					
THYROID and PARATHYROID		NC	NC	NC	NC
THYMUS		0.281/0.232	0.287/0.256	0.278/0.263	0.284/0.268
OVARIES		0.127/0.110	0.115/0.094	0.111/0.124	0.114/0.096
UTERUS		NC	NC	NC	NC

Absolute weights are expressed as mean (grams). Entries in table are expressed both as organ weight from animals taken at the end of the terminal phase and recovery phase of the study (main phase organ weight/recovery phase organ weight).

Table 8: Female's organ weight (study # 1)

At study day 27 of recovery, heart weight was increased 28% in group 4 females. At study day 37, spleen weight was increased 16% and 15% in groups 2 and 4 females, respectively. At study day 27 of recovery, thymus weight was increased 13% and 16% in groups 3 and 4 females, respectively. Ovary weight was decreased 13% in group 3 at study day 37. Ovary weight was increased 13% in group 3 at study day 27 of recovery.

Gross pathology:

No test article-related effect on the macroscopic findings were reported.

Group	Males				Females			
	1	2	3	4	1	2	3	4
Animals examined	10	10	10	10	10	10	10	10
GLAND, LACRIMAL, EXTRAORBITAL Abnormal surface	-	1	-	-	-	-	-	-
GLAND, LACRIMAL, INTRAORBITAL Abnormal size	-	-	-	-	1	-	1	-
GLAND, SEMINAL VESICLE Abnormal size	-	-	1	1				
KIDNEY Abnormal color	-	-	-	-	-	-	-	1
LIVER Abnormal color	-	-	-	-	-	-	-	1

Group	Males				Females			
	1	2	3	4	1	2	3	4
Animals examined	10	10	10	10	10	10	10	10
LYMPH NODE, DRAINING	-	1	-	-	-	-	2	-
Abnormal color								
Abnormal size	-	-	1	5	-	1	1	3
LYMPH NODE, INGUINAL	-	1	-	-	-	-	-	-
Abnormal color								
OVARY					-	-	-	1
Cyst								
THYMUS	-	-	2	-	2	-	-	1
Abnormal color								
ESOPHAGUS	-	-	-	-	-	-	-	1
Abnormal shape								

Table 9: Gross pathology results (study # 1); sponsor provided

Microscopic findings are listed below:

Group	Males				Females			
	1	2	3	4	1	2	3	4
Animals examined	10	10	10	10	10	10	10	10
Sperm granuloma in epididymis	-	1	-	-				
Harderian gland	-	-	-	-	-	-	2	3
Minimal mononuclear cell infiltration								
Cyst in pituitary gland	-	1	-	-	1	1	-	-
Heart	1	-	-	1	-	-	-	-
Minimal myocardium inflammatory cell infiltrate								
Kidney								
Minimal mononuclear cell Infiltration	1	-	-	-	-	-	-	-
Minimal tubular basophilia	1	-	-	1	-	-	-	-
Liver	-	-	-	-	-	1	-	-
Minimal periportal hepatocyte deposition pigment								
Minimal mononuclear cell infiltration	3	3	1	2	3	1	1	3
Lungs								
Minimal alveolar histiocytosis	1	-	2	-	-	-	2	-
Minimal epithelium: alveolus hyperplasia	1	-	1	1	-	-	-	-
Minimal alveolus inflammation	-	-	-	1	-	-	-	-
Draining lymph nodes								
Macrophage accumulation;								
Minimal	-	7	-	9	-	5	-	8
mild	-	3	-	1	-	5	-	2
Mild sinus erythrocytosis	-	1	-	-	-	-	-	-
Germinal center increased cellularity								
Minimal	-	2	2	5	6	2	4	2
mild	-	-	2	3	1	1	2	4
Inguinal lymph node	-	-	-	1	-	-	-	-
Minimal macrophage accumulation								
Mild sinus erythrocytosis	-	1	-	-	-	-	-	-
Mesenteric lymph node								
Minimal erythrocytosis	-	-	1	-	-	-	-	-
Oviduct	-	-	-	-	-	-	-	1
Hemorrhage								
Pancreas	-	1	-	-	-	-	-	1
Minimal mononuclear cell infiltration								

Group	Males				Females			
	1	2	3	4	1	2	3	4
Animals examined	10	10	10	10	10	10	10	10
Injection site								
Muscle chronic active inflammation								
Minimal	9	1	6	-	9	-	9	-
Mild	-	9	-	1	-	10	-	2
moderate	-	-	-	9	-	-	-	8
Skin	-	-	-	-	1	-	1	-
Minimal epithelium acanthosis								
Thymus	1	1	2	-	1	-	-	1
Minimal hemorrhage								
Lacrimal gland								
Minimal mononuclear cell infiltration	4	1	-	-	1	-	-	1
Harderian metaplasia								
Minimal	-	3	2	4	2	2	3	2
mild	-	2	2	1	-	-	-	-

Table 10: Microscopic findings (study # 1); sponsor provided

An extensive number of tissues were examined for histology. The inflammation at the injection sites is due to the injection procedure. Draining lymph node findings might be related to test article-related immune responses. No increased incidences of histological findings indicative of potential adverse events were reported in the treated groups relative to the controls.

Chronic active inflammation at the injection site was reported in all groups at the end of the dosing phase. This chronic active inflammation was characterized predominantly by accumulations of macrophages admixed with lymphocytes, plasma cells and polymorphonuclear cells. Multifocal intralesional aggregates of degenerating neutrophils were reported in group 4. The severity was greater in groups 2 and 4 (contains Al(OH)₃) compared to groups 1 and 3 (treated with saline or PF-07052944 without Al(OH)₃). Animals treated with Al(OH)₃ had granular material within the injection site both within and outside of macrophages (interpreted to be accumulated Al[OH]₃). Chronic active inflammation at the injection site was fully recovered in groups 1 and 3 (without Al(OH)₃). However, it was partially recovered in group 4 (treated with PF-07052944 and Al(OH)₃) and unchanged in group 2 (Al(OH)₃ control). This finding is a typical inflammatory response to vaccine antigen and/or aluminum-containing formulations (6), with some contribution of mechanical trauma due to the injection.

Increased cellularity in germinal centers of the draining lymph nodes was reported in all groups. This increase was generally reported at a higher incidence in animals administered PF-07052944 with or without Al(OH)₃. This increase might be related to immune activation typical of immunostimulants (7, 8). Accumulation of macrophages in the draining lymph nodes of groups 2 and 4 was also reported. These findings were not reported in groups 3 and 4 males and in group 3 females at the end of the recovery period. Partial recovery in group 4 females was reported. However, accumulation of macrophages in the draining lymph node did not recover in groups 2 and 4 animals.

The greater severity of injection site inflammation in group 4 animals was associated with higher mean neutrophil count (1.56x and 2.16x in males and females, respectively). It was also

associated with the increased acute phase proteins (higher mean fibrinogen [1.36x and 1.63x in males and females, respectively], higher mean globulin [1.09x] with resultant lower AG ratio [0.91x]. The inflammation was also associated with higher mean alpha 2-macroglobulin [2.16x] in females and decreased albumin in males (a negative acute phase protein) (lower mean albumin [0.97x] with resultant lower albumin: globulin [AG] ratio [0.92x] in males), compared with the Al(OH)₃ control group.

Local toxicity:

No test article-related effects on injection sites were reported

Body temperature:

No test article-related effects on body temperature were reported.

Serology:

Using RSV A and RSV B viral microneutralization assays, antibody responses to RSV formulations PF-07052944 were assessed. Geometric mean titers (GMT) were reported in this assay. The serum samples were tested according to Pfizer's SOP VR-TM-10216 and results reviewed according to VR-SOP-LC-11141. The pairwise geometric mean ratio (GMR) and 95% CI were calculated for each study group to evaluate the GMT fold-rise from PID day 11 to days 36 and 38 in the dosing phase, and days 8/7 (males/females) and 28/27 (males/females) in the recovery phase.

Test article-related immune responses to RSV A and RSV B were reported in group 4 (PF-07052944 formulated in Al(OH)₃). Group 3 males elicited an immune response to RSV A and RSV B at day 36 of the dosing phase. However, females did not elicit an immune response at any time point.

Adjuvanted (with Al(OH)₃) vaccine showed higher immune responses than the unadjuvanted vaccine. No immune responses to RSV A or RSV B were reported in the saline and Al(OH)₃ control groups (groups 1 and 2).

In conclusion, immune responses to RSV A and RSV B were reported in the adjuvanted vaccine groups. A low functional antibody response to RSV A and RSV B were reported in males treated with PF-07052944 without Al(OH)₃.

RSV Subgroup	Study Group	Gender	Phase	Time Point (Day)	N	Geometric Mean Titer	Lower 95% Bound	Upper 95% Bound
RSV A	1	Male	PID	11	15	68	50	92
			Dosing	36	15	84	67	107
			Dosing	38	15	45	32	63
			Recovery	8	5	57	25	144
			Recovery	28	5	30	25	51
		Female	PID	11	15	71	50	100
			Dosing	36	15	55	37	80
			Dosing	38	15	49	36	68
			Recovery	7	5	40	25	91
			Recovery	27	5	25	25	25
	2	Male	PID	11	15	82	59	114
			Dosing	36	13	65	46	94

RSV Subgroup	Study Group	Gender	Phase	Time Point (Day)	N	Geometric Mean Titer	Lower 95% Bound	Upper 95% Bound
			Dosing	38	15	37	28	50
			Recovery	8	5	94	68	129
			Recovery	28	5	36	25	67
		Female	PID	11	15	48	34	68
			Dosing	36	15	44	32	61
			Dosing	38	15	25	25	25
			Recovery	7	5	25	25	25
			Recovery	27	5	25	25	25
	3	Male	PID	11	15	66	49	88
			Dosing	36	15	323	181	574
			Dosing	38	13	124	57	268
			Recovery	8	5	282	155	514
			Recovery	28	5	136	34	545
		Female	PID	11	15	25	25	25
			Dosing	36	14	31	25	51
			Dosing	38	15	38	25	70
			Recovery	7	5	44	25	204
			Recovery	27	4	25	25	25
	4	Male	PID	11	15	69	48	98
			Dosing	36	15	14090	9758	20344
			Dosing	38	15	13095	9223	18591
			Recovery	8	5	28083	10855	72650
			Recovery	28	5	21944	13809	34872
		Female	PID	11	15	25	25	25
			Dosing	36	15	24030	16179	35691
			Dosing	38	15	21121	12977	34375
			Recovery	7	5	59659	31181	114144
			Recovery	27	5	52283	39297	69561
RSV B	1	Male	PID	11	15	35	35	35
			Dosing	36	15	35	35	35
			Dosing	38	15	35	35	35
			Recovery	8	5	35	35	35
			Recovery	28	5	35	35	35
		Female	PID	11	15	35	35	35
			Dosing	36	15	35	35	35
			Dosing	38	15	35	35	35
			Recovery	7	5	35	35	35
			Recovery	27	5	35	35	35
	2	Male	PID	11	15	35	35	35
			Dosing	36	15	35	35	35
			Dosing	38	15	35	35	35
			Recovery	8	5	35	35	35
			Recovery	28	5	35	35	35
		Female	PID	11	15	35	35	35
			Dosing	36	15	37	35	42
			Dosing	38	15	35	35	35
			Recovery	7	5	35	35	35
			Recovery	27	5	35	35	35
	3	Male	PID	11	15	35	35	35
			Dosing	36	12	109	44	273
			Dosing	38	13	57	35	102
			Recovery	8	4	75	35	857
			Recovery	28	3	35	35	35
		Female	PID	11	15	35	35	35
			Dosing	36	14	35	35	35
			Dosing	38	14	35	35	35
			Recovery	7	5	35	35	35
			Recovery	27	5	35	35	35

RSV Subgroup	Study Group	Gender	Phase	Time Point (Day)	N	Geometric Mean Titer	Lower 95% Bound	Upper 95% Bound
	4	Male	PID	11	15	37	35	40
			Dosing	36	15	12722	8382	19310
			Dosing	38	15	11727	7948	17305
			Recovery	8	5	32644	10960	97229
			Recovery	28	5	23677	7765	72195
		Female	PID	11	15	35	35	35
			Dosing	36	14	24596	18184	33268
			Dosing	38	14	19135	14587	25101
			Recovery	7	5	41370	25830	66262
			Recovery	27	5	24748	11583	52877

Table 11: RSV A and RSV B neutralization responses in test animals by subtype, study group, gender and time point (study # 1); sponsor provided

Test article related effects are listed in the table below:

Test article related effects	Effects considered incidental
↑ Monocytes in females ↑ Neutrophils ↓ Basophils ↑ LUC in females Injection site findings Microscopic draining lymph node findings Immune responses	↑ Heart weight

Table 12: Test article-related effects (study # 1)

Assessment:

No treatment-related, mortality, nor any toxicologically relevant changes in clinical signs, food consumption, body weight, body temperature, injection sites findings, ophthalmoscopic parameters, or gross pathology were reported.

Monocytosis could be indicative of the intended immune response or could be secondary to muscle damage at the site of injection as an indication of inflammation and repair.

Neutrophils are key components in the system of defense against infection. An individual with absence or scarcity of neutrophils (neutropenia) is vulnerable to infection. Basophils play a role in both parasitic infections and allergies. Basopenia has been reported in association with autoimmune urticaria.

LUC is a measurement of the large, peroxidase-negative cells which cannot be further characterized (i.e. as large lymphocytes, virocytes, or stem cells) present in a biological specimen. In LUC are found large lymphoid cells, more immature lymphocytes and other cells. If the value is higher than normal, blood counts should be checked under a microscope slide.

An increase in heart weight (28%) was reported in group 4 females at study day 27 of recovery. This increase was reported with high standard deviation (0.39) when compared to groups 1, 2, and 3 (0.05, 0.04, and 0.06, respectively). This increase was due to an outlier (animal number 120 in group 4 recovery). Absolute heart weight for this animal was 1.6 grams compared to the

other 4 animals heart weights (0.6, 0.7, 0.8, and 0.8 grams) in this group. This increase was not reported in males and was not considered of toxicological value.

Injection site findings might be related to an inflammatory response to vaccine antigen and/or aluminum-containing formulations (6), with some contribution of mechanical trauma due to the injection.

The microscopic draining lymph node findings might be related to immune activation typical of immunostimulants (7, 8).

Immune responses in animals treated with the test article were reported.

Based on the overall findings in this study, it can be concluded that in (b) (4) rats, repeated administration of PF-07052944 vaccine had no adverse effects in terms of systemic toxicity.

GLP study deviations or amendments: No significant deviations or amendments were recorded that influenced the quality, integrity, or interpretation of the results.

Investigators Brochure: Having read and evaluated the Investigators Brochure, is it a fair, objective and reasonable summary of the toxicology data – yes (X) or no ().

Conclusions:

Based on nonclinical toxicity assessments, there are no significant safety issues reported in this study.

Study number 2:

Title and study number: Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of RSV Bivalent Vaccine Formulations by Intramuscular Administration in the Rabbit. Study Number: AB22373.

Performing laboratory: (b) (4)

Study initiation date: September 07, 2018

Final report date: June 12, 2019

Test article batch/lot:

<u>Test article</u>	<u>Lot No.</u>	<u>Expiration Date</u>	<u>Purity %</u>
Vaccine PF-07203723	00708311-0220-LyoDP	12/12/2018	NR
Lyophilized formulation PF-07203728	00708311-0219-LyoMatrix	12/12/2018	NR
Al(OH) ₃ PF-06928316	17-002894	08/31/2019	NR
0.9% Sodium Chloride	609587	09/30/2019	NR
0.9% Sodium Chloride	803639	02/28/2021	NR

NR = Not reported.

Animal species and strain: (b) (4) rabbit

Breeder/supplier: (b) (4)

Number of animals per group and sex: 176 virgin females (88 caesarean and 88 littering females) and 24 males (used for mating only)

Age: 16-18 weeks old for females and 20-23 weeks old for males

Body weight range: Females: 3126 to 4587 g. Males before the start of mating with littering/caesarean subgroup: 3169 to 4177 g/3313 to 4581 g.

Route and site of administration: Intramuscular (IM)

Volume of injection: The dose volume was 500 µL per animal.

Frequency of administration and study duration: Animals were dosed on study days M-21, M-7 (before the start of mating phase) and on gestation days G10 and G24.

Dose: 240 µg/day.

Stability: Analysis of stability, homogeneity and concentration of the test article under test conditions was not performed as part of the study. Stability studies were performed by the sponsor of the IND. Expiration date is 21 December 2018 (6 months from manufacture date under specified storage conditions).

Means of administration: Intramuscular (IM)

Report status: Final

Experimental design:

Animals were randomized and assigned to 4 different groups. Each group consisted of 22 animals/subgroup. Animals were dosed by intramuscular route on study days M-21, M- 7 (before the start of mating phase) and on gestation days G10 and G24. The details of the study design are listed in the following table:

Table of the experimental design

Group number	Group ^a	Dose (µg of PF-07203723 (847A and 847B)/ dosing day) ^b (µg/occasion)	Dose volume IM administration (mL)	Dosing days	Number of females	
					Littering subgroup	Caesarean subgroup
1	0.9 % Sterile Saline Control	0	0.5	M-21, M-7, G10 and G24	22	22
2	Al(OH) ₃ Control ^c	0	0.5		22	22
3	PF-07203723 without Al(OH) ₃ ^d	240	0.5		22	22
4	PF-07203723 with Al(OH) ₃ ^e	240	0.5		22	22

Al(OH)₃ : Aluminum hydroxide; IM: Intramuscular; RSV: Respiratory syncytial virus.

^a: Only female animals were administered dosing material.

^b: PF-07203723: Lyophilized RSV bivalent drug product that, after reconstitution, was composed of 480 µg/mL (240 µg/mL (b) (4) and 240 µg/mL (b) (4) in 15 mM Tris, (b) (4), 37.5 mM NaCl, 0.015% Polysorbate 80, 2.25% sucrose, 4.5% mannitol).

^c: Upon reconstitution of lyophilized matrix with Al(OH)₃ it was composed of 0.4 mg/mL aluminum as aluminum hydroxide formulated in 15 mM Tris, (b) (4), 37.5 mM NaCl, 0.015% polysorbate 80, 2.25% sucrose, 4.5% mannitol.

^d: Reconstituted with sterile water for injection.

^e: Reconstituted with 0.4 mg/mL aluminum as Al(OH)₃ in water.

Table 13: Experimental design (study #2)

Methods:**Randomization procedure:** Yes.**Statistical analysis plan:** Yes.

The following parameters were evaluated:

Parameter	Frequency
Morbidity/Mortality	Twice daily
Detailed Clinical Observations:	Once daily for clinical signs. On each day of administration, the females were observed at least three times a day (before and at least twice after administration, including once approximately 4 hours (± 1 hour) after the last animal in each group was dosed). The offspring were observed daily from postnatal day (PND) 0.
Local Tolerance	Injection sites were examined daily (once before and once after injection, then until the disappearance of any signs).
Body Weight:	<ul style="list-style-type: none"> - At least once pretest (days -8 and -4 before the first administration for the littering subgroup and day -7 before the first administration for the Cesarean subgroup) - Weekly during the premating phase including each day of administration (-21 and -7 prior to mating) - On days 0, 6, 10, 13, 16, 20, 24, 27, and 29 of gestation and day 34 of presumed gestation for the littering sub-group only (not reported) - On days 4, 7, 11, 14, 17, 21, 28, and 35 of lactation (littering subgroup only).
Food Consumption:	Daily for the periods: <ul style="list-style-type: none"> - Days 1 to 7, 7 to 14, 14 to 21, and 1 to 21 during the pre-mating period. - Days 0 to 6, 6 to 10, 10 to 13, 13 to 16, 16 to 20, 20 to 24, 24 to 27, 27 to 29, and 0 to 29 of gestation. - Days 0 to 4, 4 to 7, 7 to 11, 11 to 14, 14 to 17, 17 to 21, 21 to 28, 28 to 35, and 0 to 35 of lactation (littering sub-group only).
Mating	The mating phase started 21 days after the first administration. Each day, up to 20 females were paired with males (1:1 ratio) of the same strain for at least 3 minutes or until copulation occurred.
Pregnancy and Parturition (Littering Subgroup)	From day 30 post-coitum, each female was observed at least 4 times a day for the onset and duration of parturition. The following information was recorded: <ul style="list-style-type: none"> - Date of parturition (day 0 of lactation or PND 0) - Duration of gestation (calculated value based on the time of onset of parturition) - Abnormalities of nesting or nursing behavior - Number of implantation sites (at necropsy).
Litter Data (Littering Subgroup)	For each litter, the following were recorded: <ul style="list-style-type: none"> - External abnormalities of the pups - Number of pups alive on PND 0, 4, 7, 11, 14, 17, 21, 28, and 35 - Weight of pups alive on PND 4, 7, 11, 14, 17, 21, 28, and 35 - Pre-weaning development of the offspring, as assessed by verification of: <ol style="list-style-type: none"> 1- pupil reflex on PND 35 2- auditory reflex on PND 35.
Immunogenicity Evaluation in Dams	<ul style="list-style-type: none"> - M-21 (before the first injection). - M1 (before mating). - G29 and L35 for the Cesarean and littering subgroups, respectively (just before necropsy).

Parameter	Frequency
Terminal Examinations: Necropsy Schedule:	<ul style="list-style-type: none"> - Cesarean subgroups: on day 29 post-coitum - Littering subgroups: on day 35 of lactation (with litter) - Unmated females were necropsied on study day 30 or 35 - Mated females that failed to litter between days 43 and 45 post-coitum.
Caesarean Examinations (Caesarean Subgroup)	<p>The ovaries and uterus were removed and examined including examination of the placentae. The following data were recorded:</p> <ul style="list-style-type: none"> - Pregnancy status - Number of corpora lutea - Number of implantations - Number and distribution of live fetuses - Number and distribution of embryonic/fetal deaths, classified as follows: <ul style="list-style-type: none"> * Early: Only placenta visible at termination * Late: Both placenta and embryonic tissue visible at termination * Dead fetus - Gravid uterus weight - Individual fetal weights
Fetal Examination (Caesarean Subgroup)	<p>Fetuses were examined visceraally and sexed at the time of Cesarean section. Following this, the head of approximately half of the fetuses in each litter was removed and fixed in Harrison's fluid for subsequent examination by serial sectioning. The eviscerated fetal carcasses were fixed and processed for skeletal examination.</p>
Necropsy of Pups (Littering Subgroup)	<p>All pups (including any moribund or found dead) were sexed by internal inspection and were given a macroscopic examination (including the thoracic, abdominal, and pelvic viscera) for structural or pathological changes.</p>
Blood Sampling of Fetuses and Pups (Caesarean and Littering Subgroups)	<ul style="list-style-type: none"> - G29 for fetuses from Cesarean subgroup. - PND 35 for pups from each available litter from littering subgroup (just before necropsy).

Table 14: Parameters evaluated (study #2)

Results:

No test article-related morbidity and/or mortality were reported.

Systemic toxicity:

No treatment-related, mortality, nor any toxicologically relevant changes in clinical signs, food consumption, or body weight findings were reported.

Mating performance and fertility:

No test article (with or without Al(OH)₃)-related effects on mating performance or fertility were reported.

In total (Caesarean and littering subgroups combined), 43, 41, 40, and 40 (out of 44) females were mated in groups 1, 2, 3, and 4, respectively. The copulation index for groups 3 and 4 (91%), was marginally lower than in group 1 (98%). However, the values in groups 3 and 4 remained within the historical control range (89% to 100%) and considered not related to test article treatment.

There were 41/43, 40/41, 39/40, and 38/40 pregnant/inseminated females in groups 1, 2, 3, and 4, respectively. The fertility index was consequently comparable in groups 1, 2, 3, and 4 at 95%, 98%, 98%, and 95%, respectively.

Summary of cohabitation data and maternal performance

GROUP	1	2	3	4
TREATMENT	0.9% Saline control	Al(OH) ₃ control	PF-07203723 without Al(OH) ₃	PF-07203723 with Al(OH) ₃
<u>LITTERING (L) AND (C) CAESAREAN SUB-GROUPS:</u>				
Paired	44	44	44	44
Failed to mate	1C	2C+1L	2C+2L	2C+2L
Inseminated	43(21C+22L)	41(20C+21L)	40(20C+20L)	40(20C+20L)
Pregnant	41(20C+21L)	40(19C+21L)	39(20C+19L)	38(19C+19L)
Not pregnant	1C+1L	1C	1L	1C+1L
COPULATION INDEX (%)	98	93	91	91
PREGNANCY RATE (%)	93	91	89	86
FERTILITY INDEX (%)	95	98	98	95
Caesarean phase (inseminated females)				
- Aborted	0	1	0	0
- With viable foetuses	20	18	20	19
Lactation phase (inseminated females)				
- Aborted	0	0	0	1
- Pregnant females that littered	21	21	19	18
- Total litter death <i>post-partum</i>	0	1	0	1
- Reared pups to weaning	21	20	19	17
GESTATION INDEX (%)	100	100	100	95

Table 15: Summary of cohabitation data and maternal performance (study #2); sponsor provided

Caesarean data

Gravid uterus of adult females

No test article (with or without Al(OH)₃)-related effects on mean gravid uterus weight were reported. In group 4, mean gravid uterus weight was slightly lower (-10%) than group 1. This is due to an incidentally slightly lower mean live litter size attributed to incidental differences in the preimplantation data.

Day(s): G29 relative to mating (litter: A)

Sex: Female		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Gravid	Mean	552.32	576.17	560.36	496.18
Uterus	SD	100.81	99.33	101.69	118.25
(g)	N	20	18	20	19
	%Diff	-	4.32	1.46	-10.16
Necropsy	Mean	4294.2	4187.7	4206.4	4199.3
BW	SD	295.7	345.3	270.6	292.2
(g)	N	20	18	20	19
	%Diff	.	-2.5	-2.0	-2.2
Adjusted	Mean	3741.84	3611.55	3645.99	3703.08
BW	SD	277.90	346.50	283.08	268.68
(g)	N	20	18	20	19
	%Diff	.	-3.48	-2.56	-1.04
Net BWC	Mean	251.10	218.78	198.40	212.00
from G6	SD	175.33	136.34	170.11	174.25
(g)	N	20	18	20	19
	%Diff	.	-12.87	-20.99	-15.57
Net BWC	Mean	-301.22	-357.39	-361.96	-284.18
- Uterine Wt	SD	175.01	135.62	125.18	171.90
(g)	N	20	18	20	19
	%Diff	.	18.65	20.17	-5.65
Mean Fetal	Mean	41.45	43.42	43.46	42.96
Wt (Both)	SD	4.23	5.94	4.11	5.64
(g)	N	20	18	20	19
	%Diff	.	4.77	4.87	3.66
No. Live	Mean	9.2	9.2	8.8	8.0
Fetuses	SD	2.0	2.3	1.5	2.4
	%Diff	.	0.8	-4.4	-12.6

1 [I - Automatic transformation: Identity (no transformation)]

Table 16: Mean gravid uterus weight and maternal body weight change (study #2); sponsor provided

Pregnancy incidence

At the terminal Caesarean examinations, there were 20, 18, 20 and 19 pregnant females from the 21, 20, 20 and 20 mated in groups 1, 2, 3, and 4, respectively. All of the pregnant females had viable fetuses.

Pre-implantation data

No test article (with or without Al(OH)₃)-related effects on the pre-implantation were reported. The mean numbers of corpora lutea and implantation sites (9.1 and 8.2, respectively) were marginally lower, and the percentage pre-implantation loss higher (10.9%) in group 4 compared with group 1 (10.1, 9.5 and 5.5%, respectively). These changes were within the historical control range (9.0 to 12.1, 8.0 to 10.9 and 2.5% to 13.0% for numbers of corpora lutea, implantations and pre-implantation loss, respectively) and considered not related to test article treatment.

Post-implantation data

No test article (with or without Al(OH)₃)-related effects on embryo-fetal survival were reported. In all groups, the mean percentage post-implantation loss was comparable. Mean live litter size was slightly lower in group 4 (8.0) compared with group 1 (9.2) due to the incidental differences

in the pre-implantation data. This value was within the historical control range for main embryo-fetal development investigations (7.7 to 10.3). Thus, it was not considered test article related.

Fetal data

No test article (with or without Al(OH)₃)-related effects on mean fetal weight were reported. No test article (with or without Al(OH)₃)-related effects on fetal sex ratio were reported.

Fetal observations

The numbers of fetuses (litters) submitted to the different examinations were as follows:

Group	1 0.9 % Sterile Saline Control	2 Vehicle Al(OH) ₃ Control	3 PF-07203723 without Al(OH) ₃	4 PF- 07203723 with Al(OH) ₃
External examination	183 (20)	166 (18)	175 (20)	152 (19)
Internal examination				
body	183 (20)	166 (18)	175 (20)	152 (19)
head	88 (20)	78 (18)	82 (20)	72 (19)
Skeletal examination				
body	183 (20)	166 (18)	175 (20)	152 (19)
head	95 (20)	88 (18)	93 (20)	80 (19)

Table 17: Numbers of fetuses (litters) submitted to the different examinations (study #2); sponsor provided

Mean Caesarean section data

Sex: Female Day(s) Relative to Mating (Litter: A)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Females Pregnant [CHSQFS]	N+ve	20	18	20	19
Dams with Viable Foetuses		20	18	20	19
No. of Corpora Lutea [GEN AN]	Mean	10.1 I ¹	10.3	9.5	9.1
	SD	1.9	1.9	1.2	1.9
	Sum	201 I ¹	186	189	172
No. of Implantations [GEN AN]	Mean	9.5 I ¹	9.7	9.1	8.2
	SD	2.1	2.3	1.4	2.4
	Sum	190 I ¹	174	182	156
Pre-Implantation Loss [GEN AN]	Mean	0.6 R ²	0.7	0.4	0.8
	SD	0.9	1.6	0.6	1.0
	Sum	11 R ²	12	7	16
Pre-Implantation Loss (%) [KWLWCX]	Mean	5.46	6.11	3.87	10.92
	SD	8.62	13.87	6.54	15.51
No. of Early Resorptions [GEN AN]	Mean	0.2 R ²	0.4	0.2	0.2
	SD	0.5	0.7	0.4	0.5
	Sum	4 R ²	7	4	3
Early Resorptions (%) [KWLWCX]	Mean	2.08	4.03	2.52	1.75

Sex: Female Day(s) Relative to Mating (Litter: A)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
No. of Late Resorptions [GEN AN]	SD	5.97	7.19	5.20	5.57
	Mean	0.2 R ²	0.1	0.2	0.1
	SD	0.5	0.2	0.5	0.2
Late Resorptions (%) [KWLWCX]	Sum	3 R ²	1	3	1
	Mean	1.39	0.46	1.41	0.58
	SD	4.37	1.96	4.54	2.55
No. of Dead Fetuses [GEN AN]	Mean	0.0 R ²	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
	Sum	0 R ²	0	0	0
Post-Implantation Loss [GEN AN]	Mean	0.4 R ²	0.4	0.4	0.2
	SD	0.7	0.7	0.6	0.5
	Sum	7 R ²	8	7	4
Post-Implantation Loss (%) [KWLWCX]	Mean	3.47	4.50	3.93	2.34
	SD	6.97	7.18	6.33	5.95
	Sum	183 I ¹	166	175	152
No. of Live Fetuses [GEN AN]	Mean	9.2 I ¹	9.2	8.8	8.0
	SD	2.0	2.3	1.5	2.4
	Sum	183 I ¹	166	175	152
No. of Male Fetuses [GEN AN]	Mean	5.3 R,k ²	4.7	4.3	3.3 dd ³
	SD	1.9	1.8	2.3	1.8
	Sum	105 R,k ²	84	85	63 dd ³
No. of Female Fetuses [GEN AN]	Mean	3.9 R ⁴	4.6	4.5	4.7
	SD	2.1	1.8	1.9	2.2
	Sum	78 R ⁴	82	90	89
Male Fetuses (%) [KWLWCX]	Mean	58.32	50.37	47.99	40.18
	SD	18.39	14.82	20.24	22.36
	Sum	376.01 I ¹	390.88	379.83	334.64
Total Litter Weight (g) [GEN AN]	SD	74.46	69.22	74.48	85.95
	N	20	18	20	19
	%Diff	.	3.95	1.02	-11.00
Mean Fetal Weight (both) (g) [GEN AN]	Mean	41.45 I ¹	43.42	43.46	42.96
	SD	4.23	5.94	4.11	5.64
	N	20	18	20	19
Mean Fetal Weight (M) (g) [GEN AN]	%Diff	.	4.77	4.87	3.66
	Mean	41.85 I ¹	43.48	44.18	43.03
	SD	4.67	6.00	5.27	5.53
Mean Fetal Weight (F) (g) [GEN AN]	Mean	40.65 I ¹	43.46	42.72	42.00
	SD	4.95	6.49	4.26	5.71
	N	20	18	20	19

[CHSQFS] - Chi-Squared & Fisher's Exact

[GEN AN] - Generalised Anova/Ancova Test

[KWLWCX] - Kruskal Wallis & Wilcoxon

1 [I - Automatic transformation: Identity (no transformation)]

2 [R,k - Automatic transformation: Rank, (all groups) Test: Kruskal-Wallis p < 0.05]

3 [dd - Test: Dunnett Non-Parametric 2-sided p < 0.01]

4 [R - Automatic transformation: Rank]

Table 18: Mean Caesarean section data (study #2); sponsor provided

External observations

No test article (with or without Al(OH)₃)-related effects on fetal external morphology were reported. In group 4, 1 fetus from a single litter was reported with paw hyperflexion. In group 1, one fetus had acaudia.

Soft tissue findings

No test article (with or without Al(OH)₃)-related effects on fetal soft tissue morphology were reported. Visceral malformations were reported in 1 (1) and 3 (2) fetuses (litters) in groups 3 and 4, respectively. This finding was reported in 4 (4) and 3 (3) of groups 1 and 2, respectively.

The fetus from group 3 (F145) had several cardiovascular changes including a ventricular septum defect, small left ventricle and a narrowed interrupted aortic arch with associated absent aortic valves that terminated in the left carotid artery. However, in two fetuses from each of group 1 (F96 and F100) and group 2 (F121 and F128), cardiovascular changes, including ventricular septum defect together with abnormalities affecting the aortic arch (dilatation) and pulmonary trunk (atresia with associated absence of the pulmonary valves) were also reported. Thus, this finding was not considered test article related. This is further supported by the presence of these types of changes in the historical control data. Abnormal lung lobation was reported in one fetus of group 3. This is a single incidence and not considered test article related.

Absent gall bladder was reported in one fetus of group 4. This finding was also reported in one group 1 fetus and is also present in the historical control data. Thus, this finding was considered incidental and to have no association with the test article. The second fetus from group 4 (from the same fetus) had a cleft palate. This malformation was considered to be incidental because it is part of the background of spontaneous findings in the strain of rabbit (one fetus in 2012) and in isolation. Malpositioned (cranially) testis was also reported in one group 4 fetus. This malformation was considered to be incidental because it is part of the background of spontaneous findings in the strain of rabbit (three fetuses between 2013 and 2015) and in isolation. In groups 3 and 4, other less severe soft tissue anomalies (such as small gall bladder, dilated renal pelvis, malpositioned and misshapen kidney and short ureter) and variations (such as absent innominate artery) were reported. These findings were considered isolated cases, or their incidences were consistent with the concurrent control group and/or the historical control data.

Summary of fetal external, visceral and skeletal observations

Exam Type: External		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Number of Fetuses Examined:		183	166	175	152
Number of Litters Examined:		20	18	20	19
Limb/Paw/Digit					
Paw, Hyperflexion - (M)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Tail					
Tail, Acaudia - (M)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)

Table 19: Summary of fetal external observations (study #2); sponsor provided

Exam Type: Visceral Body (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-AI without	Vaccine-AI with
Number of Fetuses Examined:		183	166	175	152
Number of Litters Examined:		20	18	20	19
Abdomen					
Abdomen, Fluid-filled - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Gall bladder					
Gall bladder, Absent - (M)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	1(5.3)
Gall bladder, Small - (A)	Fetuses N(%)	0(0.0)	0(0.0)	2(1.1)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	2(10.0)	1(5.3)
Gall bladder, Supernumerary - (A)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Heart					
Aortic valve, Absent - (M)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Heart, Ventricular septum defect - (M)	Fetuses N(%)	2(1.1)	2(1.2)	1(0.6)	0(0.0)
	Litters N(%)	2(10.0)	2(11.1)	1(5.0)	0(0.0)
Pulmonary valve, Absent - (M)	Fetuses N(%)	2(1.1)	1(0.6)	0(0.0)	0(0.0)
	Litters N(%)	2(10.0)	1(5.6)	0(0.0)	0(0.0)
Ventricle, Small - (M)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Kidney					
Kidney, Dilated renal pelvis - (A)	Fetuses N(%)	0(0.0)	1(0.6)	1(0.6)	0(0.0)
Kidney (Continued...)					
Kidney, Dilated renal pelvis - (A)	Litters N(%)	0(0.0)	1(5.6)	1(5.0)	0(0.0)
Kidney, Malpositioned - (A)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	2(1.3)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	2(10.5)
Kidney, Misshapen - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.3)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	2(10.5)
Liver					
Lobe, Cyst - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Lung					
Lobe, Absent - (A)	Fetuses N(%)	11(6.0)	5(3.0)	8(4.6)	1(0.7)
	Litters N(%)	7(35.0)	4(22.2)	2(10.0)	1(5.3)
Lobe, Cyst - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	1(5.3)
Lung, Abnormal lobation - (M)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Major blood vessel					
Aortic arch, Dilated - (M)	Fetuses N(%)	2(1.1)	2(1.2)	0(0.0)	0(0.0)
	Litters N(%)	2(10.0)	2(11.1)	0(0.0)	0(0.0)
Aortic arch, Interrupted - (M)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Major blood vessel (Continued...)					
Common carotid trunk, Absent - (V)	Fetuses N(%)	45(24.6)	50(30.1)	45(25.7)	39(25.7)
	Litters N(%)	14(70.0)	13(72.2)	17(85.0)	12(63.2)
Innominate artery, Absent - (V)	Fetuses N(%)	0(0.0)	0(0.0)	2(1.1)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	2(10.0)	0(0.0)

Exam Type: Visceral Body (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Number of Fetuses Examined:		183	166	175	152
Number of Litters Examined:		20	18	20	19
Pulmonary trunk, Atresia - (M)	Fetuses N(%)	2(1.1)	1(0.6)	0(0.0)	0(0.0)
	Litters N(%)	2(10.0)	1(5.6)	0(0.0)	0(0.0)
Subclavian artery, Malpositioned - (A)	Fetuses N(%)	0(0.0)	1(0.6)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	1(5.6)	1(5.0)	0(0.0)
Subclavian artery, Retroesophageal - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	1(5.3)
Ovary					
Ovary, Cyst - (A)	Fetuses N(%)	0(0.0)	2(2.4)	0(0.0)	1(1.1)
	Litters N(%)	0(0.0)	2(11.1)	0(0.0)	1(5.3)
Ovary, Malpositioned - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Testis					
Testis, Absent - (M)	Fetuses N(%)	1(1.0)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Testis, Malpositioned - (M)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(1.6)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)
Ureter					
Ureter, Convoluted - (A)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Ureter, Retrocaval - (A)	Fetuses N(%)	9(4.9)	8(4.8)	5(2.9)	6(3.9)
	Litters N(%)	8(40.0)	6(33.3)	4(20.0)	5(26.3)
Ureter, Short - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Vein					
Azygos vein, Transposed - (A)	Fetuses N(%)	2(1.1)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)

Table 20: Summary of fetal visceral body observations (study #2); sponsor provided

Exam Type: Visceral Head (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Number of Fetuses Examined:		88	78	82	72
Number of Litters Examined:		20	18	20	19
Eye					
Retina, Fold - (M)	Fetuses N(%)	0(0.0)	1(1.3)	0(0.0)	0(0.0)
	Litters N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
Buccal cavity					
Buccal cavity, Cleft palate - (M)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(1.4)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)

Table 21: Summary of fetal visceral head observations (study #2); sponsor provided

Skeletal findings

No test article (with or without Al(OH)₃)-related effects on fetal skeletal morphology were reported. Skeletal malformations were reported in 2 (2) and 1 (1) fetus (litters) of groups 3 and 4, respectively. This is compared to the skeletal malformations which were reported in 3 (2) and 2 (1) of groups 1 and 2, respectively.

Fused sternbrae was reported in one fetus of group 4. However, fused sternbrae were also reported in two fetuses of group 1 and one fetus of group 2. This malformation was also reported in the historical control data. Thus, this finding was considered not to be related to test article treatment. In group 3, both malformed fetuses had multiple abnormalities of the thoracic vertebrae leading to a lateral shift of the vertebral column. These abnormalities were not considered test article-related because they were also present in group 1 and they were part of the background of changes for the strain of rabbit.

Misshapen caudal vertebrae were reported in one fetus of each of groups 3 and 4. The fetus in group 4 also had misshapen scapulae and misshapen 6th sternbrae. Misshapen caudal vertebra, sternbrae, and scapula are all part of the background of spontaneous findings in the strain of rabbit (5, 4 and 1 cases of misshapen caudal vertebrae, sternbrae, and scapula, respectively, between 2007 and 2012). Thus, they were considered to be incidental and not related to test article.

In groups 3 and 4, other less severe skeletal anomalies (such as less than 14 caudal vertebrae and fused cervical centrum) and variations (such as incomplete ossification of the 6th sternbrae) were reported. These isolated cases were not reported in both groups, and they were consistent with the concurrent control group and/or the historical control data. Thus, they were not considered test article related.

Summary of skeletal findings

Exam Type: Skeletal Head (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Number of Fetuses Examined:		95	88	93	80
Number of Litters Examined:		20	18	20	19
Skull					
Cranium, Sutural bone - (A)	Fetuses N(%)	0(0.0)	2(2.3)	1(1.1)	1(1.3)
	Litters N(%)	0(0.0)	2(11.1)	1(5.0)	1(5.3)
Fontanelle, Large - (A)	Fetuses N(%)	1(1.1)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Fontanelle, Small - (A)	Fetuses N(%)	0(0.0)	5(5.7)	1(1.1)	0(0.0)
	Litters N(%)	0(0.0)	2(11.1)	1(5.0)	0(0.0)
Hyoid, Misshapen - (A)	Fetuses N(%)	0(0.0)	1(1.1)	0(0.0)	1(1.3)
	Litters N(%)	0(0.0)	1(5.6)	0(0.0)	1(5.3)
Nasal, Unossified line - (A)	Fetuses N(%)	0(0.0)	1(1.1)	0(0.0)	0(0.0)
	Litters N(%)	0(0.0)	1(5.6)	0(0.0)	0(0.0)
Parietal, Unossified line - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(1.3)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Presphenoid, Incomplete ossification - (A)	Fetuses N(%)	1(1.1)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Forepaw					
Metacarpal, Incomplete ossif., 2nd to 5th	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Metacarpal, Unossified, 1st digit - (V)	Fetuses N(%)	1(0.5)	0(0.0)	1(0.6)	2(1.3)
	Litters N(%)	1(5.0)	0(0.0)	1(5.0)	2(10.5)
Phalanx, Incomplete ossification, proximal - (V)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	2(1.3)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	1(5.3)
Phalanx, Unossified, middle - (V)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	2(1.3)

Exam Type: Skeletal Head (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-AI without	Vaccine-AI with
Number of Fetuses Examined:		95	88	93	80
Number of Litters Examined:		20	18	20	19
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
General					
Vertebra, Multiple abnormalities - (M)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Hindpaw					
Tarsal bone, Unossified - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Pectoral girdle					
Scapula, Misshapen - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Pelvic girdle					
Pelvic girdle, Malpositioned - (A)	Fetuses N(%)	8(4.4)	12(7.2)	7(4.0)	5(3.3)
	Litters N(%)	6(30.0)	8(44.4)	6(30.0)	4(21.1)
Pelvic girdle (Continued...)					
Pubis, Incomplete ossification - (A)	Fetuses N(%)	3(1.6)	1(0.6)	0(0.0)	2(1.3)
	Litters N(%)	2(10.0)	1(5.6)	0(0.0)	2(10.5)
Ribs					
Ribs, Detached - (A)	Fetuses N(%)	7(3.8)	6(3.6)	6(3.4)	1(0.7)
	Litters N(%)	6(30.0)	4(22.2)	5(25.0)	1(5.3)
Ribs, Interrupted - (A)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Ribs, Misshapen - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Ribs, Nodulated - (A)	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Ribs, Number of full ribs = 12/12 - (V)	Fetuses N(%)	111(60.7)	96(57.8)	103(58.9)	92(60.5)
	Litters N(%)	20(100.0)	17(94.4)	19(95.0)	18(94.7)
Ribs, Number of full ribs = 12/13 - (V)	Fetuses N(%)	24(13.1)	26(15.7)	23(13.1)	21(13.8)
	Litters N(%)	13(65.0)	14(77.8)	14(70.0)	10(52.6)
Ribs, Short - (A)	Fetuses N(%)	15(8.2)	15(9.0)	17(9.7)	15(9.9)
	Litters N(%)	9(45.0)	13(72.2)	11(55.0)	9(47.4)
Ribs, Supernumerary cervical - (A)	Fetuses N(%)	0(0.0)	4(2.4)	7(4.0)	3(2.0)
	Litters N(%)	0(0.0)	3(16.7)	3(15.0)	2(10.5)
Ribs, Supernumerary lumbar - (A)	Fetuses N(%)	28(15.3)	24(14.5)	33(18.9)	23(15.1)
Ribs (Continued...)					
Ribs, Supernumerary lumbar - (A)	Litters N(%)	15(75.0)	11(61.1)	17(85.0)	12(63.2)
Sternebra					
Sternebra, Asymmetric - (A)	Fetuses N(%)	3(1.6)	1(0.6)	0(0.0)	0(0.0)
	Litters N(%)	2(10.0)	1(5.6)	0(0.0)	0(0.0)
Sternebra, Extra ossification site - (A)	Fetuses N(%)	1(0.5)	0(0.0)	1(0.6)	2(1.3)
	Litters N(%)	1(5.0)	0(0.0)	1(5.0)	2(10.5)
Sternebra, Fused - (M)	Fetuses N(%)	2(1.1)	2(1.2)	0(0.0)	1(0.7)
	Litters N(%)	2(10.0)	1(5.6)	0(0.0)	1(5.3)
Sternebra, Incomplete ossification, 1st/3rd -	Fetuses N(%)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)
Sternebra, Minor fusion - (A)	Fetuses N(%)	2(1.1)	5(3.0)	3(1.7)	0(0.0)
	Litters N(%)	2(10.0)	2(11.1)	3(15.0)	0(0.0)

Exam Type: Skeletal Head (Rabbit)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Number of Fetuses Examined:		95	88	93	80
Number of Litters Examined:		20	18	20	19
Sternebra, Misshapen - (A)	Fetuses N(%)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.3)
Sternebra, Unossified, 5th - (V)	Fetuses N(%)	23(12.6)	27(16.3)	17(9.7)	18(11.8)
	Litters N(%)	11(55.0)	10(55.6)	7(35.0)	7(36.8)
Sternebra, Unossified, 6th - (V)	Fetuses N(%)	7(3.8)	2(1.2)	0(0.0)	3(2.0)
	Litters N(%)	4(20.0)	2(11.1)	0(0.0)	2(10.5)
Sternebra, Incomplete ossification, 2nd/4th - (V)	Fetuses N(%)	3(1.6)	0(0.0)	1(0.6)	1(0.7)
	Litters N(%)	3(15.0)	0(0.0)	1(5.0)	1(5.3)
Sternebra (Continued...)					
Sternebra, Incomplete ossification, 6th - (V)	Fetuses N(%)	9(4.9)	4(2.4)	13(7.4)	11(7.2)
	Litters N(%)	7(35.0)	4(22.2)	5(25.0)	6(31.6)
Vertebra					
Caudal, Malpositioned - (A)	Fetuses N(%)	1(0.5)	1(0.6)	0(0.0)	2(1.3)
	Litters N(%)	1(5.0)	1(5.6)	0(0.0)	2(10.5)
Caudal, Misshapen - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	1(5.3)
Caudal, Number < 14 - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	1(0.7)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	1(5.3)
Cervical, Fused centrum - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Cervical, Small centrum - (A)	Fetuses N(%)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
	Litters N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)
Lumbar, Number = 6 - (V)	Fetuses N(%)	48(26.2)	32(19.3)	31(17.7)	35(23.0)
	Litters N(%)	14(70.0)	14(77.8)	15(75.0)	12(63.2)
Lumbar, Number = 8 - (V)	Fetuses N(%)	3(1.6)	7(4.2)	4(2.3)	4(2.6)
	Litters N(%)	3(15.0)	4(22.2)	3(15.0)	2(10.5)
Thoracic, Incomplete ossification of centrum, 1st to 9th - (A)	Fetuses N(%)	0(0.0)	1(0.6)	0(0.0)	1(0.7)
	Litters N(%)	0(0.0)	1(5.6)	0(0.0)	1(5.3)
Thoracic, Multiple abnormalities - (M)	Fetuses N(%)	0(0.0)	0(0.0)	2(1.1)	0(0.0)
Vertebra (Continued...)					
Thoracic, Multiple abnormalities - (M)	Litters N(%)	0(0.0)	0(0.0)	2(10.0)	0(0.0)
Thoracic, Number = 12 - (V)	Fetuses N(%)	111(60.7)	96(57.8)	103(58.9)	92(60.5)
	Litters N(%)	20(100.0)	17(94.4)	19(95.0)	18(94.7)

Table 22: Summary of skeletal findings (study # 2); sponsor provided

Delivery and litter data*Parturition and gestation length*

In groups 1, 2, 3, and 4, there were 21, 21, 19 and 18 pregnant females completely delivered, respectively. All females had live born pups. In all groups, the mean duration of gestation was comparable (approximately 31 days).

Pre-birth loss

No test article (with or without Al(OH)₃)-related effects on pre-birth loss were reported. The mean numbers of implantation sites and pups delivered per litter in test article treated groups

[with or without Al(OH)₃] were comparable with, or superior to, those in the saline control group.

Pup viability and litter sizes

No test article (with or without Al(OH)₃)-related effects on pup viability and litter size in the littering subgroup were reported. The mean live litter size at birth in the test article treated groups [with or without Al(OH)₃] was comparable with, or superior to, that in the saline control group. The live birth index was consequently comparable in all groups (between 96.9% and 98.0%) and consistent with the mean historical control value (96.2). Thereafter (between PND 1 to PND 35), pup mortality was slightly higher in groups 4 (18 pups from 8 litters) and 2 (25 pups from 13 litters) when compared with groups 1 and 3 (11 and 14 pups from 8 and 7 litters each, respectively). In each group, the total mortality count was influenced by a female that incurred total litter death of 5 or 6 pups post-partum (F29 in group 2 and F81 in group 4). However, this is considered incidental because such cases of total litter death post-partum are present in the historical control data. In addition, both the viability and lactation indices in groups 4 and 2 remained consistent with group 1 and/or within the historical control ranges (91.1% to 100%, and 84.5% to 94.4%, respectively). Mean live litter size in test article treated groups at weaning was superior to that in group 1.

Summary of delivery and litter data

Sex: Female		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine -Al with
Day(s) Relative to Littering (Litter: A)					
Females Completing Delivery [CHSQFS]	N+ve	21	21	19	18
with Liveborn Pups [CHSQFS]	N+ve	21	21	19	18
with Stillborn Pups [CHSQFS]	N+ve	3	4	4	3
with all Stillborn Pups [CHSQFS]	N+ve	0	0	0	0
with all Dead PND 35 [CHSQFS]	N+ve	0	1	0	1
Gestation Length (Days) [GEN AN]	Mean	31.6 R ¹	31.2	31.6	31.3
	SD	0.7	0.4	0.6	0.5
	N	21	21	19	18
Number of Implantation Sites [GEN AN]	Mean	8.1 I ²	9.8	9.4	8.4
	SD	2.3	2.4	2.0	2.5
	N	21	21	19	18
	Sum	171 I ²	205	179	151
Pre-Birth Loss (%) [GEN AN]	Mean	4.88 R ¹	2.14	6.23	3.79
	SD	8.58	6.25	9.03	9.81
	N	21	21	19	18
Pups Delivered/Litter [GEN AN]	Mean	7.7 I _a ³	9.5	8.8	8.1
	SD	2.0	2.0	2.1	2.6
	N	21	21	19	18
	Sum	161 I _a ³	199	168	145
Live Pups PND 0 [GEN AN]	Mean	7.4 I _a ¹	9.3	8.6	7.9
	SD	2.3	1.9	1.9	2.5
	N	21	21	19	18
	Sum	156 I _a ¹	195	164	142
Live Pups PND 4 [GEN AN]	Mean	7.2 R _k ³	9.0	8.4	7.8
	SD	2.2	1.9	1.8	2.5
	N	21	21	19	17

Sex: Female Day(s) Relative to Littering (Litter: A)		Saline Control	Al(OH) ₃ Control	Vaccine- Al without	Vaccine -Al with
Live Pups PND 7 [GEN AN]	Sum	152 R,k ³	190 ^{1,4}	160	133
	Mean	7.1 ⁵	9.1 ^{1,4}	8.1	7.6
	SD	2.1	1.5	1.6	2.5
	N	21	20	19	17
Live Pups PND 11 [GEN AN]	Sum	149 ⁵	181 ^{1,4}	153	129
	Mean	7.0 ⁵	8.9 ^{1,4}	8.0	7.4
	SD	2.1	1.4	1.5	2.3
	N	21	20	19	17
Live Pups PND 14 [GEN AN]	Sum	148 ⁵	177 ^{1,4}	152	126
	Mean	7.0 ⁵	8.9 ^{1,4}	8.0	7.4
	SD	2.1	1.4	1.5	2.3
	N	21	20	19	17
Live Pups PND 17 [GEN AN]	Sum	148 ⁵	177 ^{1,4}	152	126
	Mean	7.0 R,k ¹	8.6 ^{d²}	8.0	7.4
	SD	2.1	1.4	1.5	2.4
	N	21	20	19	17
Live Pups PND 21 [GEN AN]	Sum	148 R,k ¹	17 ^{d²}	152	125
	Mean	7.0 R,k ¹	8.6 ^{dd³}	7.9	7.3
	SD	2.0	1.4	1.4	2.4
	N	21	20	19	17
Live Pups PND 28 [GEN AN]	Sum	146 R,k ¹	17 ^{dd³}	150	124
	Mean	6.9 R,k ¹	8.5 ^{dd³}	7.9	7.3
	SD	2.0	1.3	1.4	2.4
	N	21	20	19	17
Live Pups PND 35 [GEN AN]	Sum	145 R,k ¹	17 ^{dd³}	150	124
	Mean	6.9 R,k ¹	8.5 ^{dd³}	7.9	7.3
	SD	2.0	1.3	1.4	2.4
	N	21	20	19	17
Dead, Miss., Cannib. PND 0 [CHSQFS]	Sum	5	4 ¹	4	3
Dead, Miss., Cannib. PND 1-7 [CHSQFS]	Sum	7	14	11	13
Dead, Miss., Cannib. PND 8-14 [CHSQFS]	Sum	1	4	1	3
Dead, Miss., Cannib. PND 15-21 [CHSQFS]	Sum	2	5	2	2
Dead, Miss., Cannib. PND 22-28 [CHSQFS]	Sum	1	2	0	0
Dead, Miss., Cannib. PND 29-35 [CHSQFS]	Sum	0	0	0	0
Dead, Miss., Cannib. PND 1-35 [CHSQFS]	Sum	11	25	14	18
Live Birth Index (%)		96.9	98.0	97.6	97.9
Viability Index (PND 0-4) (%)		97.4	97.4	97.6	93.7
Lactation Index (PND 4-35) (%)		95.4	89.5	93.8	93.2
Sex Ratio PND 35- % Males [CHSQFS]	Mean	46.7	53.7	47.7	52.7

[CHSQFS] - Chi-Squared & Fisher's Exact [GEN AN] - Generalised Anova/Ancova test

[GEN AN] - Generalised Anova/Ancova test

1 [I,a - Automatic Transformation: Identity (No Transformation), (All Groups) Test: Analysis of V

2 [d - Test: Dunnett 2-Sided p < 0.05]

3 [R,k - Automatic Transformation: Rank, (All Groups) Test: Kruskal-Wallis p < 0.05]

4 [dd - Test: Dunnett Non-Parametric 2-Sided p < 0.01]

5 [R,kk - Automatic Transformation: Rank, (All Groups) Test: Kruskal-Wallis p < 0.01]

6 [ddd - Test: Dunnett Non-Parametric 2-Sided p < 0.001]

Table 23: Summary of delivery and litter data (study #2); sponsor provided

Pup observations

No test article (with or without Al(OH)₃)-related effects on pup clinical observations were reported.

Pup weights

No test article (with or without Al(OH)₃)-related effects on mean pup weight were reported. Mean values in groups 2, 3, and 4 tended to be slightly lower than in group 1 from birth to weaning. However, this was due to a relatively high mean pup weight throughout lactation in group 1 compared with the mean historical control values.

Mean pup body weight (grams)

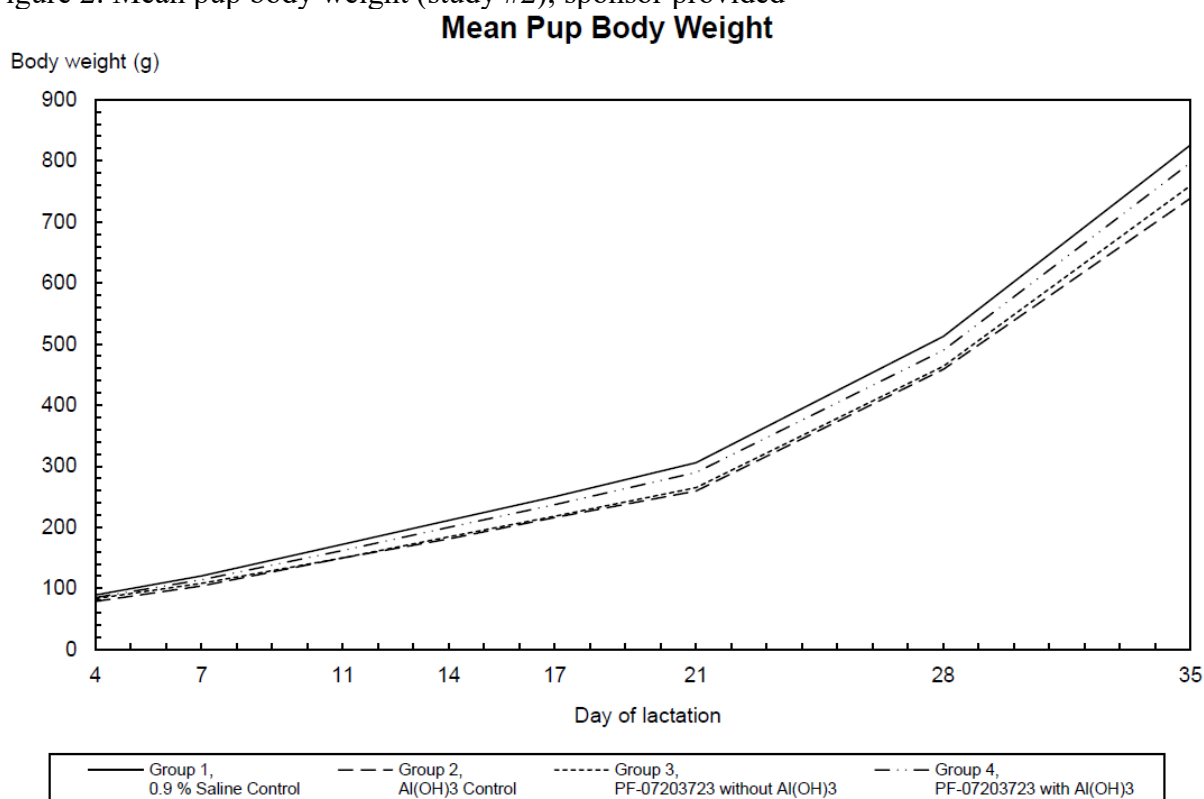
Sex: Female Day(s) Relative to Littering (Litter: A)		Saline Control	Al(OH) ₃ Control	Vaccine-Al without	Vaccine-Al with
Mean Pup Body Weight d4 [GEN AN]	Mean	89.57 R ¹	78.66	83.36	85.13
	SD	21.11	12.99	13.32	14.56
	N	21	21	19	17
	%Diff	.	-12.18	-6.93	-4.95
Mean Pup Body Weight d7 [GEN AN]	Mean	120.70 R ¹	104.11	108.32	114.30
	SD	34.48	18.10	15.74	22.38
	N	21	20	19	17
	%Diff	.	-13.74	-10.25	-5.30
Mean Pup Body Weight d11 [GEN AN]	Mean	172.50 R ¹	150.02	149.88	162.04
	SD	49.06	29.42	25.50	28.36
	N	21	20	19	17
	%Diff	.	-13.03	-13.12	-6.06
Mean Pup Body Weight d14 [GEN AN]	Mean	211.43 R ¹	181.19	184.57	200.02
	SD	64.40	30.72	30.20	42.19
	N	21	20	19	17
	%Diff	.	-14.30	-12.70	-5.40
Mean Pup Body Weight d17 [GEN AN]	Mean	250.17 R ¹	216.30	218.36	237.33
	SD	82.33	35.30	35.75	52.54
	N	21	20	19	17
	%Diff	.	-13.54	-12.71	-5.13
Mean Pup Body Weight d21 [GEN AN]	Mean	305.68 R ¹	259.34	264.76	289.74
	SD	104.31	40.52	42.83	70.92
	N	21	20	19	17
	%Diff	.	-15.16	-13.39	-5.22
Mean Pup Body Weight d28 [GEN AN]	Mean	512.32 R ¹	453.80	463.85	489.97
	SD	140.64	63.39	70.09	94.37
	N	21	20	19	17
	%Diff	.	-11.42	-9.46	-4.36
Mean Pup Body Weight d35 [GEN AN]	Mean	825.97 R ¹	738.49	759.29	796.91
	SD	170.52	79.69	99.16	126.97
	N	21	20	19	17
	%Diff	.	-10.59	-8.07	-3.52

[GEN AN] - Generalised Anova/Ancova test

1 [R - Automatic Transformation: Rank]

Table 24: Mean pup body weight (grams) (study #2); sponsor provided

Figure 2: Mean pup body weight (study #2); sponsor provided

*Pup functional development*

No test article (with or without Al(OH)₃)-related effects on the pre-weaning functional reflexes (pupil and auditory reflexes) were reported.

Summary of reflex and physical development

Group	1	2	3	4
			PF-07203723	
Dose level	Saline Control	Al(OH) ₃ Control	without Al(OH) ₃	PF-07203723 with Al(OH) ₃
PUPILLARY REFLEX - PND 35				
- % of pups positive:	100	100	100	100
AUDITORY REFLEX - PND 35				
- % of pups positive:	100	100	100	100

Table 25: Summary of reflex and physical development (study #2); sponsor provided

Pup necropsy findings

No test article (with or without Al(OH)₃)-related effects on pup macroscopic findings were reported.

Maternal Macroscopic findings

No test article (with or without Al(OH)₃)-related effects on maternal macroscopic findings were reported. Cysts in ovaries/oviducts and/or alopecia were occasionally reported. These low incidence findings were considered incidental because they were isolated in nature across all groups.

Summary of maternal macroscopic observations

		FEMALES			
Removal Reason: TERMINAL SACRIFICE		Saline Control	Al (OH)3 Control	Vaccine-Al without	Vaccine-Al with
Number of Animals on Study :		21	19	20	20
Number of Animals Completed:		(21)	(19)	(20)	(20)
OVARIES;					
Submitted.....		(0)	(0)	(0)	(1)
No Visible Lesions.....		0	0	0	0
Cyst; several; left		0	0	0	1
OVIDUCTS;					
Submitted.....		(0)	(1)	(0)	(1)
No Visible Lesions.....		0	0	0	0
Cyst; several; left		0	1	0	0
Cyst; single; left		0	0	0	1
SKIN/SUBCUTIS;					
Submitted.....		(1)	(0)	(1)	(0)
No Visible Lesions.....		0	0	0	0
Alopecia; single; forelimb; hindlimb; right; left		0	0	1	0
Alopecia; right; forelimb		1	0	0	0
GALLBLADDER;					
Submitted.....		(1)	(0)	(0)	(0)
No Visible Lesions.....		0	0	0	0
Small		1	0	0	0
OVIDUCTS;					
Submitted.....		(2)	(2)	(1)	(1)
No Visible Lesions.....		0	0	0	0
Cyst; several; right; left		0	0	0	1
Cyst; several; left		2	2	0	0
Cyst; single; right		2	0	1	0
UTERUS;					
Submitted.....		(0)	(2)	(0)	(2)
No Visible Lesions.....		0	0	0	0
Cyst; several; horn; left		0	1	0	0
Cyst; single; horn; right		0	1	0	1
Cyst; single; horn; left		0	0	0	1
DRAINING LYMPH NODES;					
Submitted.....		(1)	(0)	(0)	(0)
No Visible Lesions.....		0	0	0	0
For external mass 1; left; deep axillary lymph nodes; skin/subcutis		1	0	0	0
For external mass 2; left; deep axillary lymph nodes; skin/subcutis		1	0	0	0
For external mass 3; right; deep axillary lymph nodes; skin/subcutis		1	0	0	0
AXILLARY LYMPH NODES;					
Submitted.....		(1)	(0)	(0)	(0)
No Visible Lesions.....		0	0	0	0
Enlarged; right; left		1	0	0	0
SKIN/SUBCUTIS;					
Submitted.....		(0)	(1)	(0)	(0)
No Visible Lesions.....		0	0	0	0
Alopecia; single; hindlimb; right; left		0	1	0	0
SKIN/SUBCUTIS;					
Submitted.....		(1)	(0)	(0)	(0)
No Visible Lesions.....		0	0	0	0
Mass 1; solid; thoracic region; homogeneous; movable; multinodular; left		1	0	0	0
Mass 2; solid; thoracic region; homogeneous; movable; left		1	0	0	0
Mass 3; solid; thoracic region; homogeneous; movable; multinodular; right		1	0	0	0

Table 26: Summary of maternal macroscopic observations (study #2); sponsor provided

Immunogenicity evaluation

The geometric mean fold rise (GMFR) and corresponding 95% CI of the GMFR calculated from initiation of dosing (M-21) to the day of cohabitation (M1) for each study group are presented in the table below. GMFRs for both control groups (1 and 2) were 1.0. The GMFRs for group 3 were 78.1 and 52.9 for RSV A and B, respectively. The GMFRs for group 4 were 406.9 and 254.6 for RSV A and B, respectively.

Subgroup	Study Group	Animal	Time Point	No. Animals	Geometric Mean Titer	Lower 95% Bound	Upper 95% Bound
RSV A	Group 1	Maternal	M-21	44	26	25	28
			M1	44	26	25	27
			G29	21	26	24	27
			L35	21	26	24	27
	Group 2	Fetus	G29	20	27	24	29
		Kits	PND35	21	25	25	25
		Maternal	M-21	44	26	24	27
			M1	44	27	25	28
			G29	19	25	25	25
			L35	20	25	25	25
	Group 3	Fetus	G29	18	28	25	31
		Kits	PND35	20	25	25	25
		Maternal	M-21	44	26	25	27
			M1	44	2006	1360	2960
			G29	20	4432	2505	7840
			L35	19	817	453	1471
	Group 4	Fetus	G29	20	4909	2971	8111
		Kits	PND35	19	156	98	247
		Maternal	M-21	44	26	25	27
			M1	44	10459	8229	13294
			G29	20	23597	18288	30446
			L35	17	5944	3706	9532
RSV B	Group 1	Maternal	G29	19	19411	15386	24487
			Kits	17	817	587	1136
			M-21	44	35	35	36
			M1	44	35	35	36
	Group 2	Maternal	G29	21	35	35	35
			L35	21	35	35	36
		Fetus	G29	20	38	34	42
		Kits	PND35	21	35	35	35
	Group 3	Maternal	M-21	44	35	35	35
			M1	44	36	35	37
			G29	19	35	35	35
			L35	20	35	35	35
	Group 4	Fetus	G29	18	36	35	37
		Kits	PND35	20	35	35	35
		Maternal	M-21	44	35	35	35
			M1	44	1851	1279	2678
			G29	20	4500	2447	8275
			L35	19	749	408	1372
	Group 5	Fetus	G29	20	4765	2783	8158
		Kits	PND35	19	149	93	238
		Maternal	M-21	44	35	35	35
			M1	44	8923	7036	11315
			G29	20	20449	15637	26743
			L35	17	6771	3998	11466
RSV C	Group 1	Fetus	G29	19	18045	14236	22874
		Kits	PND35	17	1031	741	1434

Table 27: RSV neutralization titers in adult female rabbits, fetuses, and kits by group and time point (study #2); sponsor provided

Subgroup	Study Group	Animal	No. Animals	Geometric Mean Fold Rise (M1/M-21)	Geometric Mean Fold Rise (95% C.I.)
RSV A	Group 1	Maternal	44	1.0	(0.9, 1.0)
	Group 2	Maternal	44	1.0	(1.0, 1.1)
	Group 3	Maternal	44	78.1	(53.2, 114.5)
	Group 4	Maternal	44	406.9	(318.6, 519.6)
RSV B	Group 1	Maternal	44	1.0	(1.0, 1.0)
	Group 2	Maternal	44	1.0	(1.0, 1.0)
	Group 3	Maternal	44	52.9	(36.5, 76.5)
	Group 4	Maternal	44	254.6	(200.7, 322.9)

Table 28: RSV neutralization titers in adult female rabbits, fetuses, and kits by group and time point (study #2); sponsor provided

Integrated summary and discussion of results

No test article (with or without Al(OH)₃)-related effects on mortality or clinical signs and no effects on body weight or food consumption before mating, or during the gestation or lactation phases were reported. No test article (with or without Al(OH)₃)-related effects on macroscopic observations were reported. No test article (with or without Al(OH)₃)-related effects on mating, fertility and pregnancy index, or any ovarian, uterine, or litter parameters, including F1 survival, growth, external, visceral, and skeletal malformations, anomalies, or variations, or effects on auditory startle or pupil constriction reflexes in the F1 pups were reported.

GLP study deviations or amendments: No significant deviations or amendments were recorded that influenced the quality, integrity, or interpretation of the results.

Investigators Brochure: Having read and evaluated the Investigators Brochure, is it a fair, objective and reasonable summary of the toxicology data – yes () or no (X).

Communication to sponsor:

The findings of this study need to be added to an amended Investigators Brochure (IB). Please add this study to your IB.

Conclusions:

Based on nonclinical toxicity assessments, there are no significant safety issues to report in this study.

Overall conclusion:

Based on nonclinical toxicity assessments, there are no significant safety issues to report.

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