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AV7909 Overview

October 2018
ACIP Meeting

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AV7909 Update
ACIP Meeting
OCTOBER 2018

Agenda

- AV7909 product overview and development timeline
- Summary of completed clinical studies
  - Immunogenicity and safety
- Non-clinical studies supporting Phase 3 clinical endpoints
  - BioThrax® (Anthrax Vaccine Adsorbed) and AV7909 toxin neutralizing antibody (TNA) thresholds of protection
- Upcoming Phase 3 and Phase 2 clinical studies
  - Study overviews
  - Proposed endpoints

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AV7909 Clinical Development

Paul-André de Lame, M.D.

Vice President, Clinical Development

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Product Overview

Description	AV7909 consists of Anthrax Vaccine Adsorbed (AVA) drug substance with CPG 7909 Adjuvant
Indication and Usage	AV7909 is being developed for post-exposure prophylaxis (PEP) of disease resulting from suspected or confirmed *Bacillus anthracis* exposure, when combined with the recommended course of antimicrobial therapy
Dosage / Administration	**Route**: Intramuscular **Volume**: 0.5 mL per dose **Dose**: 0.5 mL AVA + 0.25 mg CPG 7909 **Schedule**: Two doses, two weeks apart

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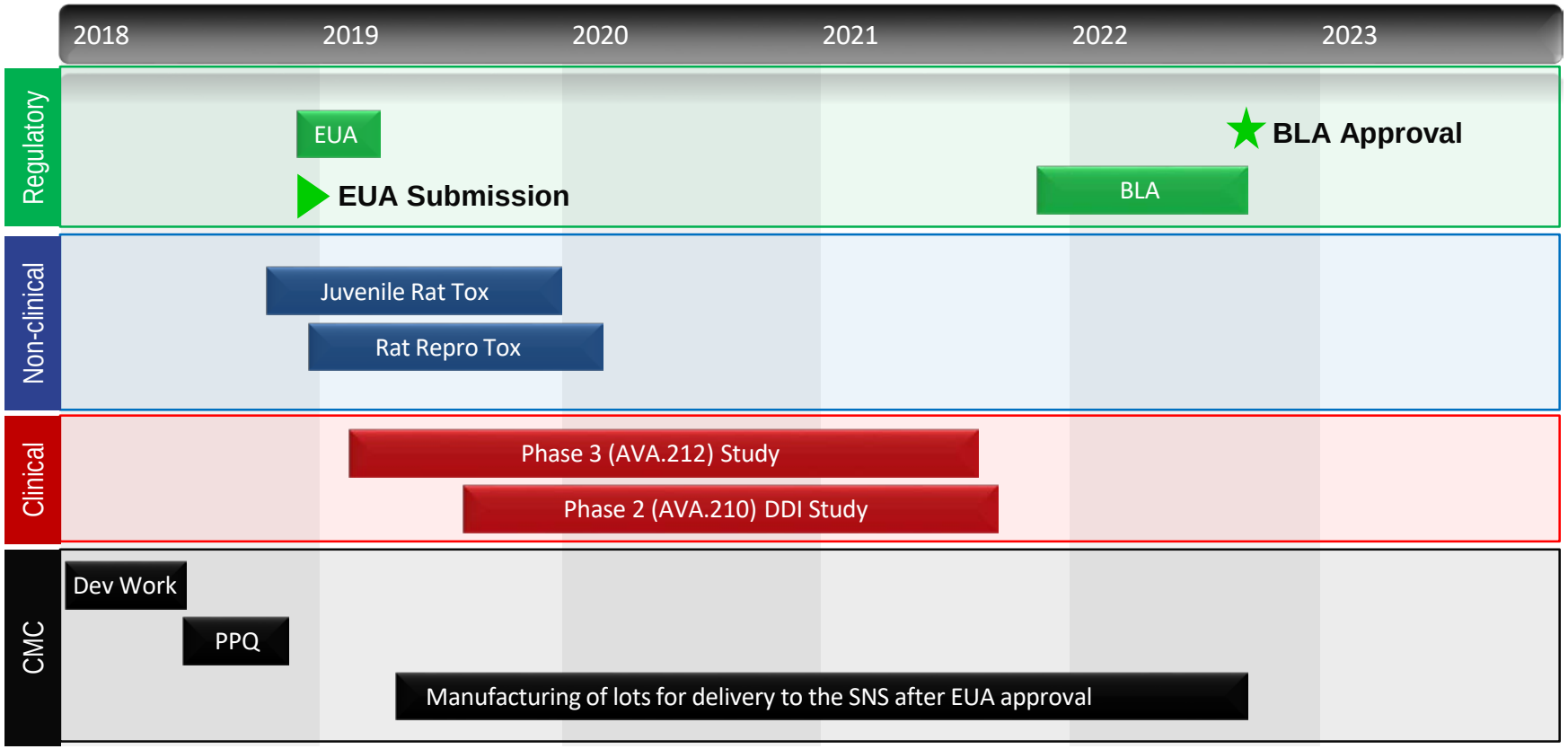
Pathway to Licensure:
Current Product Development Plan



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Clinical Development:
AV7909 has demonstrated safety and immunogenicity in 244 adults

	Study Title	Sample Size	Receiving AV7909	Summary of Major Findings
2005	Phase 1a: BioThrax/ CPG 7909 admixture	69	24	• Demonstrated a significantly increased and accelerated immune response for BioThrax/CPG 7909 admixture versus BioThrax vaccine alone and CPG 7909 alone
2014	Phase 1b: Safety and Immunogenicity Study	105	75	• Demonstrated an accelerated and enhanced immune response for all four formulations • Safety and immunogenicity data allowed for selection of final formulation (0.5 mL AVA BDS and 0.25 mg CPG 7909) for further development
2015	Phase 2: Dose Confirmation and Schedule Study	168	145	• Safety and immunogenicity data allowed for selection of a two-dose PEP schedule with final formulation for AV7909 (days 1 and 15) • Vaccinations in all groups were well tolerated, with no serious adverse events assessed as potentially vaccine-related
	Total	**342**	**244**	

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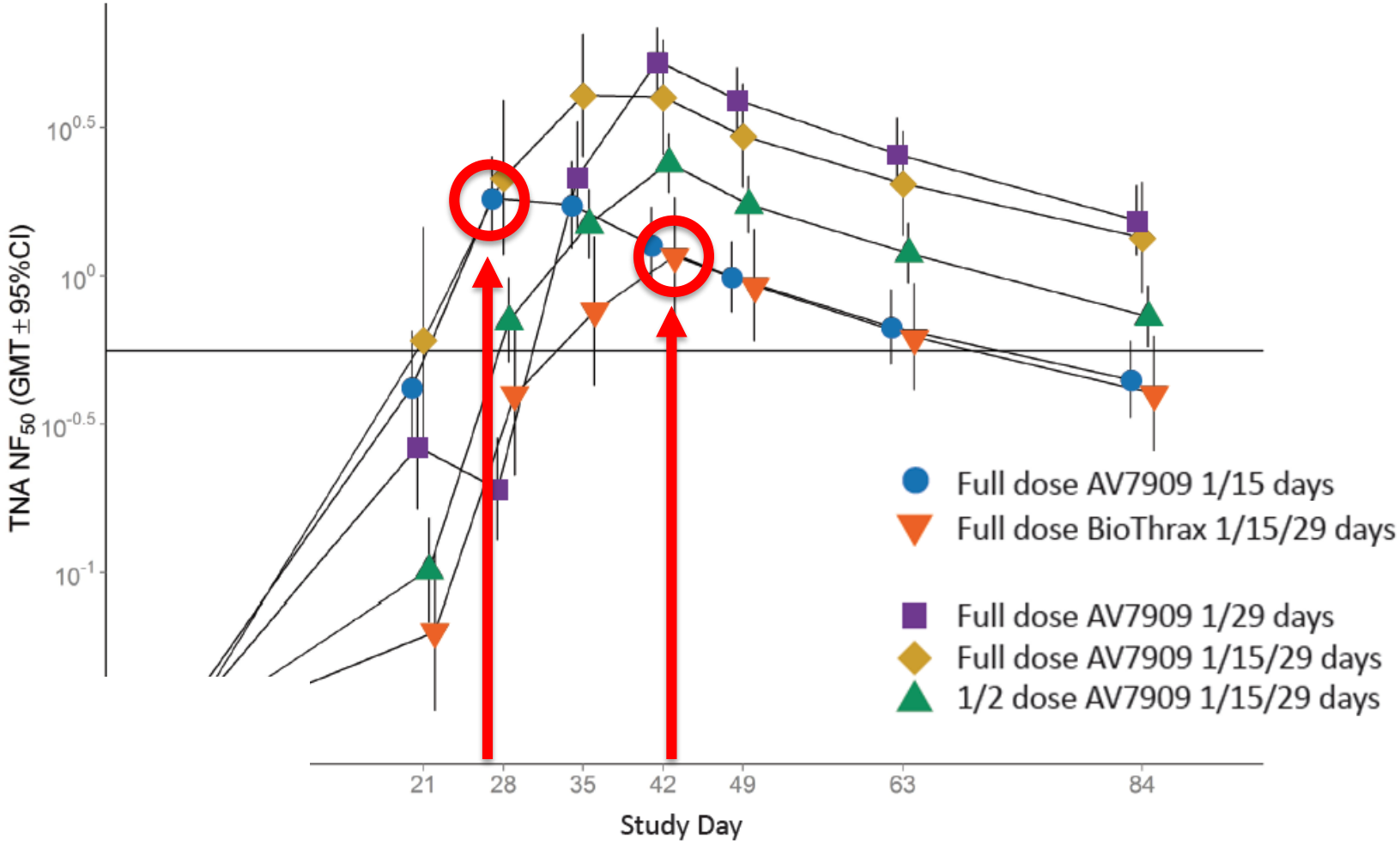
Phase 2 Study:

Immunogenicity data informed selection of a two-dose PEP schedule for AV7909 (1/15 days)



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Where Are We at this Point?

1. Post Phase 2 Conclusions

i. Analysis of the AV7909 TNA threshold of protection data revealed that addition of the CPG 7909 adjuvant to BioThrax® (Anthrax Vaccine Adsorbed, AVA) improved the kinetics and magnitude of the immune response

ii. Two-dose AV7909 (IM) is found to be comparable to three-dose BioThrax vaccine (IM) at Day 63

iii. Safety profile of AV7909 is similar to that of BioThrax vaccine

2. Next Studies Leading to Licensure

i. Protocol AVA-212: Phase 3 Lot-to-Lot Consistency

ii. Protocol AVA-210: Phase 2 Drug-Drug Interaction Study

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Non-clinical Studies: Analysis of the Antibody Threshold of Protection for BioThrax Vaccine and AV7909

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Jeffry Shearer MS, PMP

Director, In Vivo Testing

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Overview of BioThrax Vaccine and AV7909 Animal Study Designs

Goal: Determine the TNA NF_{50} Threshold of Protection Associated with 70% Probability of Survival

	BioThrax Vaccine		AV7909	
Animal Models	Rabbits: New Zealand White *n*=632	Non-human Primates (NHP): cynomolgus macaques *n*=307		Guinea Pigs (GP) *n*=409
Vaccination Schedules	Days 0 & 28		**Days 0 & 14** –*or*- Days 0 & 28	
Vaccination Dilutions	Various dilutions of vaccine used to stratify the immune response prior to challenge			
Challenge Schedule(s)	Day 70		**Day 28** –*or*- Day 70	
Challenge Model	200 LD_{50} aerosolized *B. anthracis* (Ames strain) spores			
Endpoints	Correlation of pre-exposure TNA NF_{50} with survival; Confirmation of death due to anthrax			

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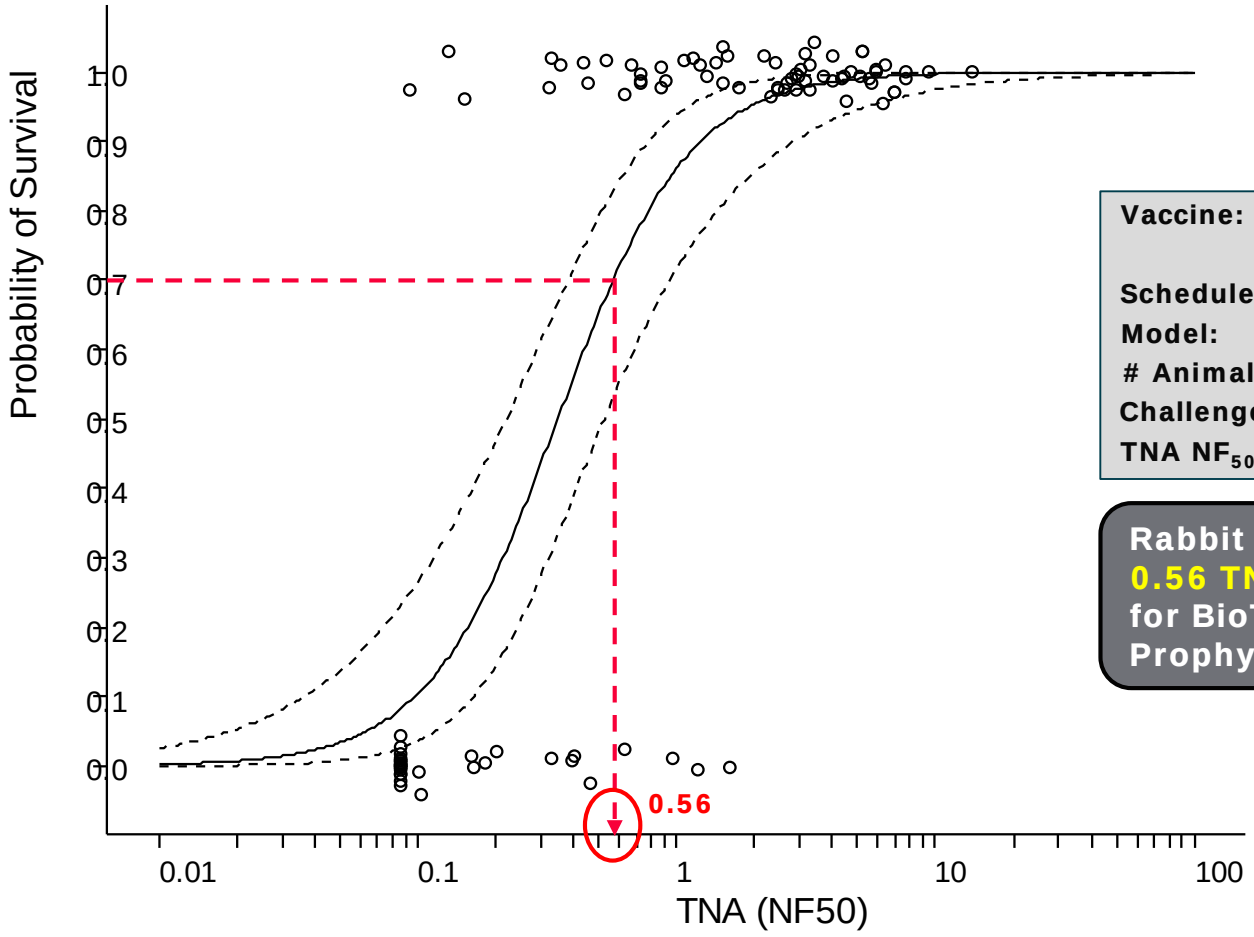
TNA Threshold of Protection
Licensure-Enabling BioThrax Vaccine Rabbit Study



Vaccine:	BioThrax (AVA) (multiple dilutions)
Schedule:	Days 0 & 28
Model:	Pre-exposure Prophylaxis (PrEP)
# Animals:	96
Challenge:	Day 70
TNA NF_{50}:	Day 69 data shown

Rabbit Study 646 set the 0.56 TNA threshold of protection for BioThrax Post-exposure Prophylaxis (PEP) Licensure

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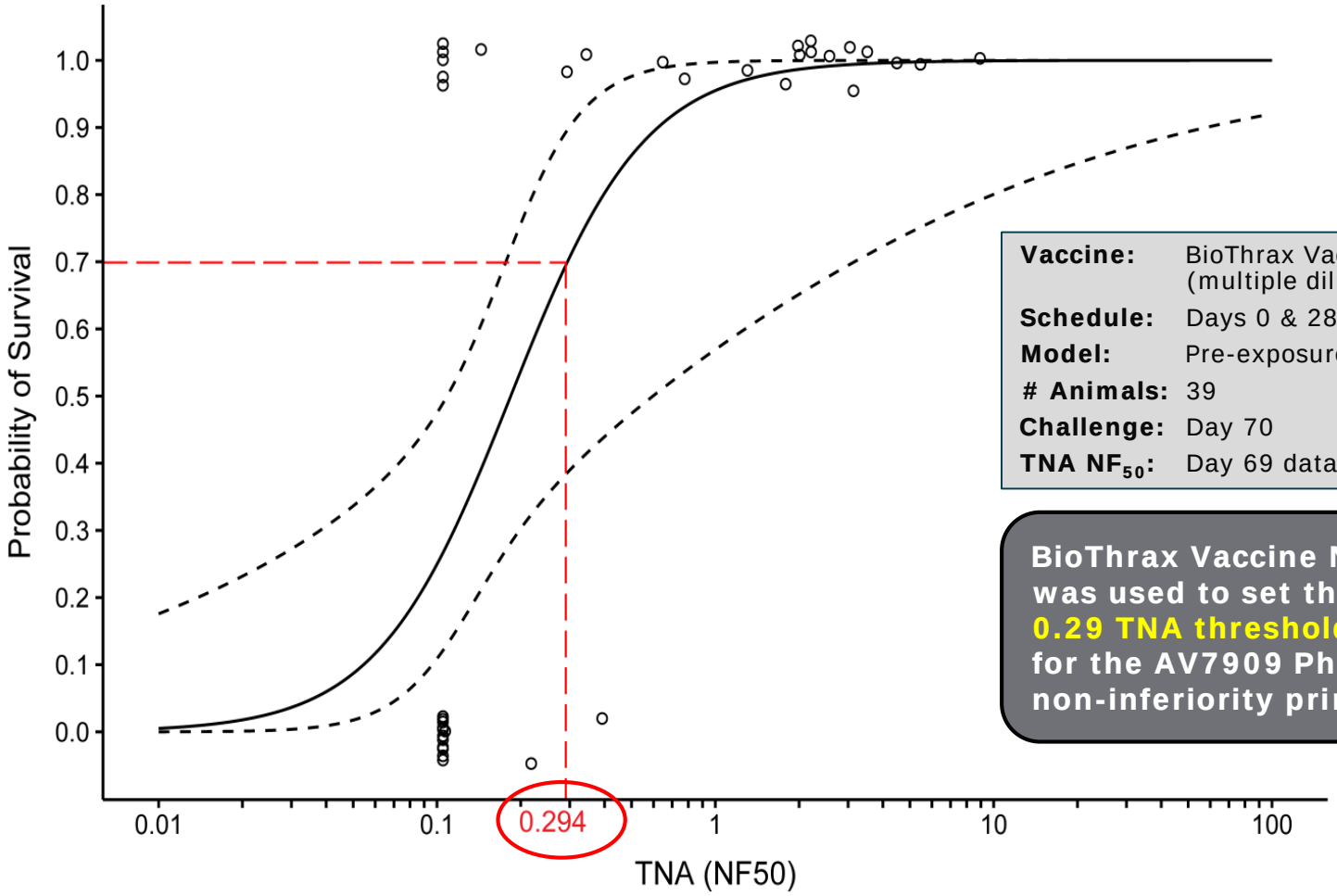
TNA Threshold of Protection
BioThrax Vaccine Non-human Primate Study



Vaccine:	BioThrax Vaccine (multiple dilutions)
Schedule:	Days 0 & 28
Model:	Pre-exposure Prophylaxis (PrEP)
# Animals:	39
Challenge:	Day 70
TNA NF_{50}:	Day 69 data shown

BioThrax Vaccine NHP Study 844 was used to set the proposed 0.29 TNA threshold of protection for the AV7909 Phase III non-inferiority primary endpoint

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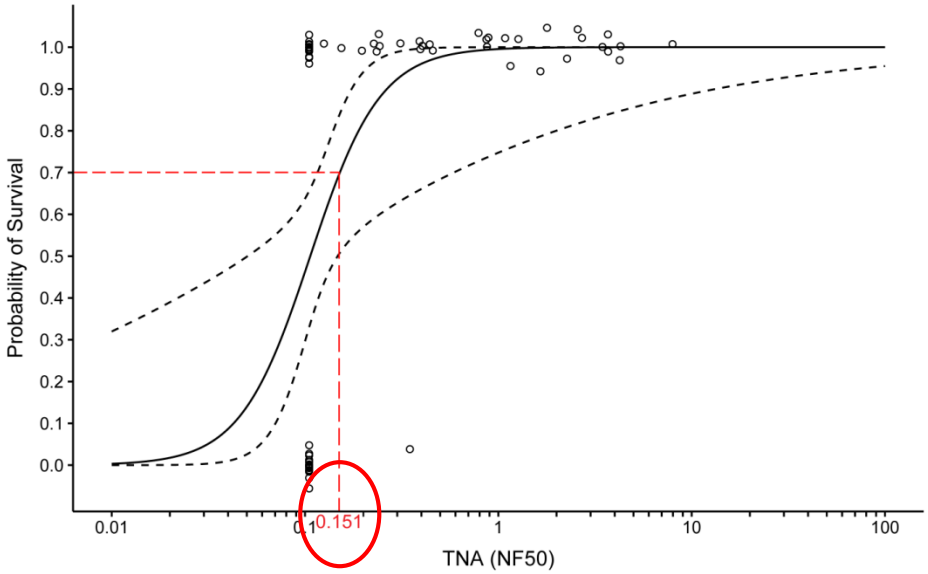
TNA Threshold of Protection

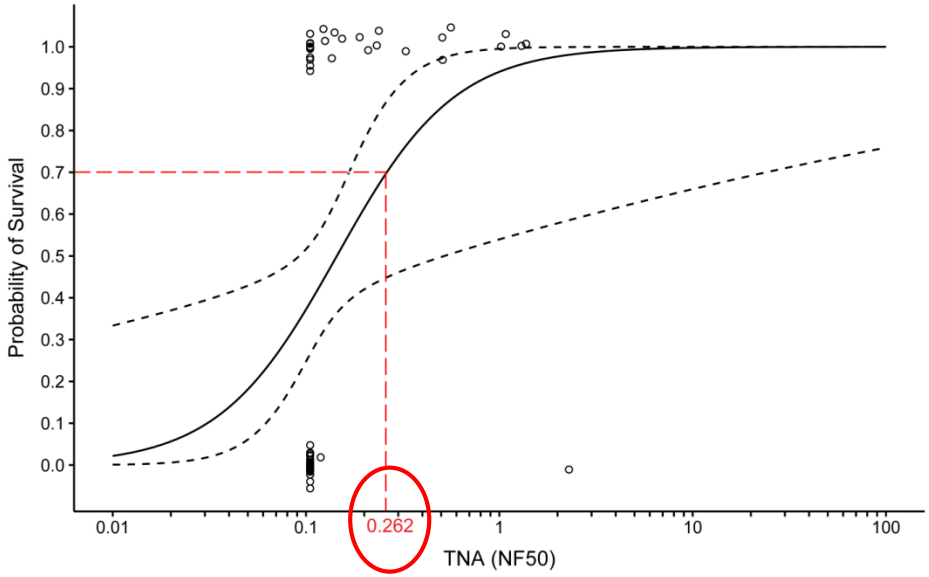
AV7909 NHP Studies: Accelerated Schedule

Challenge: Day 28



0.151

Challenge: Day 70



0.262

Vaccine:	AV7909 (multiple dilutions)
Schedule:	Days 0 & 14
Model:	Pre-exposure Prophylaxis (PrEP)
# Animals:	64 in each challenge group
Challenge:	Day 28 or 70

AV7909 NHP Study 3655 was used to set the proposed 0.15 TNA threshold of protection for the AV7909 Phase III secondary endpoint

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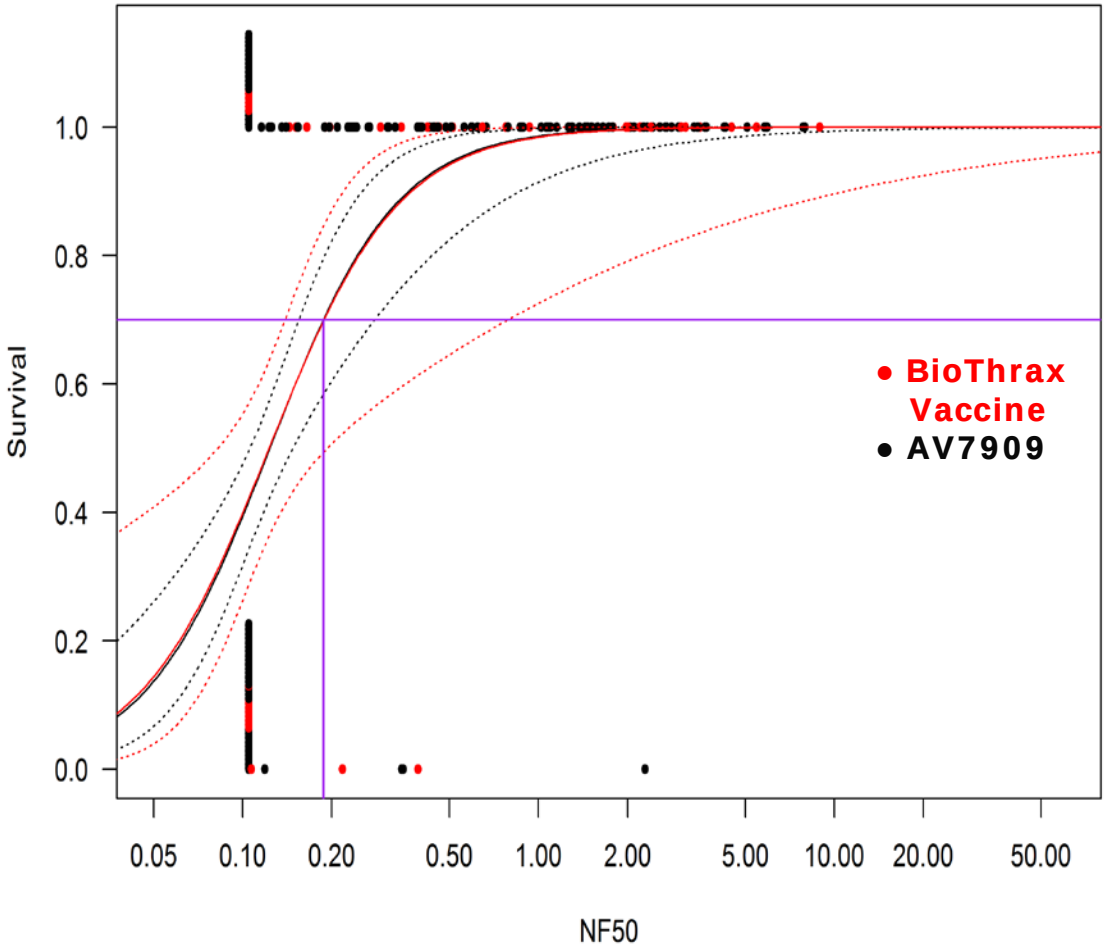
TNA Threshold of Protection
Similar for BioThrax Vaccine & AV7909 in NHPs



Vaccine:	BioThrax Vaccine (multiple dilutions)
Schedule:	Days 0,28
Challenge:	Day 70
# Animals:	72
TNA NF_{50}:	0.188
95% CI:	(0.122, 0.292)

Vaccine:	AV7909 (multiple dilutions)
Schedule:	Pooled Days 0,14 & 0,28
Challenge:	Pooled Day 28 & Day 70
# Animals:	235
TNA NF_{50}:	0.188
95% CI:	(0.146, 0.241)

TNA threshold of protection is similar for BioThrax Vaccine and AV7909 regardless of vaccination or challenge schedule

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Non-clinical Efficacy Studies Complete

Current data set sufficient to support Phase 3 endpoints

FDA U.S. FOOD & DRUG ADMINISTRATION

Date: August 21, 2018

APPROVED
By Taruna Khurana, Ph.D. at 3:18 pm, Aug 21, 2018

From: Division of Vaccines & Related Product Applications
Office of Vaccines Research & Review
Center for Biologics Evaluation & Research
Food & Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

CBER Response

CBER concurs that the guinea pig and non-human primate studies conducted to date (Study No. 3580-100069467, Study No. 968-G882407, Study No. 2940-100027634, Study No. 3655-100072763, Study No. 970-G882407 and Study No. 3124-100043225) are sufficient to support the proposed Phase 3 endpoints. Additional confirmatory animal studies are not required.

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TNA Threshold of Protection
Summary of Studies Driving Clinical Endpoints

Vaccine	Species	Vaccination Schedule	# of Animals	Challenge Day	TNA NF_{50}	(95% CI)	Phase 3 Endpoints
BioThrax	Rabbit	0, 28	96	70	**0.564**	(0.37; 0.85)	Co-Primary
BioThrax	NHP	0, 28	39	70	**0.294**	(0.14; 0.61)	Co-Primary
AV7909	GP	0, 28	200	70	**0.063**	(0.02; 0.23)	
AV7909	NHP	0, 28	107	70	**0.180**	(0.12; 0.27)	
AV7909	GP	0, 14	107	28	**0.062**	(NA)	
			106	70	**0.081**	(0.068,0.141)	
AV7909	NHP	0, 14	64	28	**0.151**	(0.116, 0.587)	Secondary
			64	70	**0.262**	(0.17; 24.34)	

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EBS.AVA.212
Phase 3 Study

A Phase 3, Randomized, Double-blind, Parallel-group Trial to Evaluate the Lot Consistency, Immunogenicity, and Safety of AV7909 for Post-exposure Prophylaxis of Anthrax in Healthy Adults

AV7909
EBS.AVA.212
Phase III Trial

Study Overview

Study Purpose

Evaluate PPQ lot consistency, immunogenicity, and safety of AV7909 in healthy adults for use in post-exposure prophylaxis of anthrax

Primary Objective

Show that three PPQ lots of AV7909 achieve a TNA $NF_{50} \geq 0.56$ on Day 64 and are non-inferior to BioThrax vaccine at Day 64

Study Design

Number of subjects: 3,850
Number of sites: 40

Group 1: AV7909 PPQ Lot #1 (N = 1,100)
Group 2: AV7909 PPQ Lot #2 (N = 1,100)
Group 3: AV7909 PPQ Lot #3 (N = 1,100)
Group 4: BioThrax (N=550)

AV7909
EBS.AVA.212
Phase III Trial

Primary Endpoints

Lot consistency (Co-primary End Points)

- Equivalent immunogenicity across three consecutive AV7909 lots as demonstrated by the 95% CI for the ratios of geometric mean TNA NF_{50} at Day 64 for each of the three lot-to-lot comparisons to be within 0.5 and 2.0
- Protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the lower-bound of the two-sided 95% CI to be ≥ 40% for the proportions of AV7909 subjects in each of the three lots achieving a **TNA NF_{50} ≥ 0.56** at Day 64

Immunogenicity at Day 64

- Lower bound of the two-sided 95% CI is ≥ 40% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥ 0.56 on Day 64
- At Day 64, ***non-inferiority*** of AV7909 to BioThrax at Day 64 as determined by the one-sided lower 95% CI of the difference in the proportion of AV7909 participants (three lots pooled) with a **TNA NF_{50} ≥ 0.29** and the proportion of BioThrax vaccine participants with a TNA NF_{50} ≥ 0.29 being greater than -15%.

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Phase III Trial

Additional Endpoints

Immunogenicity (Secondary)

- Lower bound of the two-sided 95% CI will be ≥ 67% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a **TNA NF_{50} ≥ 0.15** on Day 29.
  (Note: The primary lot consistency and immunogenicity endpoints must all be met for testing to proceed to the secondary endpoint.)

Safety

- Primary: Incidences of SAEs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination
- *Incidences of AEs from the time of the first vaccination on Day 1 through Day 64*
- *Incidences of clinical laboratory abnormalities*
- *Incidences of autoimmune-associated AESIs from the time of the first vaccination on Day 1 through the 12-month safety follow up telephone call following the last vaccination*
- *Incidences of solicited systemic reactions and solicited injection site reactions by severity following each vaccination as reported in participant e-diaries*

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EBS.AVA.210
Phase 2 DDI Study

A Phase 2 Drug-Vaccine Interaction Study to Examine Whether Co-administering AV7909 with Ciprofloxacin or Doxycycline Affects Antibiotic Pharmacokinetics or AV7909 Immunogenicity in Healthy Adults

AV7909
EBS.AVA.210
Phase II Trial

Study Overview

Study Purpose

To evaluate the pharmacokinetic (PK) profiles of ciprofloxacin or doxycycline when co-administered with AV7909 in healthy adults

Study Design

Number of subjects: 210

Group 1: AV7909 + ciprofloxacin with ciprofloxacin PK (N = 40)
Group 2: AV7909 + ciprofloxacin without ciprofloxacin PK (N = 30)
Group 3: AV7909 + doxycycline with doxycycline PK (N = 40)
Group 4: AV7909 + doxycycline without doxycycline PK (N = 30)
Group 5: AV7909 only (N = 70)

AV7909
EBS.AVA.210
Phase II Trial

Study Endpoints

Primary Endpoints

- Area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) for ciprofloxacin on Days 8 and 35
- Area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) for doxycycline on Days 8 and 38

Secondary Endpoints

Safety:

- Incidence of AEs from the first dose of any IP through the Final Study Visit (Day 45 ± 1)
- Incidence of serious AEs (SAEs) from the first dose of any IP until the 12-month follow-up (Day 388 ± 14)
- Incidence of solicited systemic and injection site reactions reported in participant e-diaries following each vaccination
- Incidence of adverse events of special interest (AESIs) from the first dose of any IP until the 12-month follow up (Day 388 ± 14)
- Incidence of clinical laboratory abnormalities

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AV7909
EBS.AVA.210
Phase II Trial

Study Endpoints

Secondary Endpoints (continued)

Pharmacokinetics and Immunogenicity:

- $AUC_{0\text{-}12h}$ and C_{max} for ciprofloxacin on Days 4 and 31 and for doxycycline on Days 2 and 32
- Geometric mean TNA 50% neutralizing factor (NF_{50}) values 2 weeks after the second vaccination (Day 37 ± 1)

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Questions?