AV7909 Overview

October 2018
ACIP Meeting
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
AV7909 Overview

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AV7909 Clinical Development

Paul-André de Lame, M.D.
Vice President, Clinical Development
# Product Overview

<table>
<thead>
<tr>
<th>Description</th>
<th>AV7909 consists of Anthrax Vaccine Adsorbed (AVA) drug substance with CPG 7909 Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication and Usage</td>
<td>AV7909 is being developed for post-exposure prophylaxis (PEP) of disease resulting from suspected or confirmed <em>Bacillus anthracis</em> exposure, when combined with the recommended course of antimicrobial therapy</td>
</tr>
</tbody>
</table>
| 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 |
Pathway to Licensure: Current Product Development Plan

### Regulatory
- **2018**: EUA Submission
- **2022**: BLA Approval

### Non-clinical
- **2018**: Juvenile Rat Tox
- **2019**: Rat Repro Tox

### Clinical
- **2020**: Phase 3 (AVA.212) Study
- **2021**: Phase 2 (AVA.210) DDI Study

### CMC
- **2019**: PPQ

- **2023**: Manufacturing of lots for delivery to the SNS after EUA approval
Clinical Development:
AV7909 has demonstrated safety and immunogenicity in 244 adults

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

Total: 342 244
Phase 2 Study:
Immunogenicity data informed selection of a two-dose PEP schedule for AV7909 (1/15 days)
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
AV7909 Overview

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

Jeffry Shearer MS, PMP
Director, In Vivo Testing
# Overview of BioThrax Vaccine and AV7909 Animal Study Designs

**Goal:** Determine the TNA NF$_{50}$ Threshold of Protection Associated with 70% Probability of Survival

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>BioThrax Vaccine</th>
<th>AV7909</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits: New Zealand White</td>
<td>Days 0 &amp; 28</td>
<td>Days 0 &amp; 14 –or- Days 0 &amp; 28</td>
</tr>
<tr>
<td>Non-human Primates (NHP): cynomolgus macaques</td>
<td>Days 0 &amp; 28</td>
<td>Days 0 &amp; 28 –or- Days 0 &amp; 28</td>
</tr>
<tr>
<td>Guinea Pigs (GP)</td>
<td>Days 0 &amp; 28</td>
<td>Days 0 &amp; 28 –or- Days 0 &amp; 28</td>
</tr>
</tbody>
</table>

- **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
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
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

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

Challenge: Day 70

AV7909 NHP Study 3655 was used to set the proposed 0.15 TNA threshold of protection for the AV7909 Phase III secondary endpoint.
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 NF50: 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 NF50: 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.
Non-clinical Efficacy Studies Complete
Current data set sufficient to support Phase 3 endpoints

Date: August 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.
## TNA Threshold of Protection
### Summary of Studies Driving Clinical Endpoints

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Species</th>
<th>Vaccination Schedule</th>
<th># of Animals</th>
<th>Challenge Day</th>
<th>TNA NF$_{50}$</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioThrax</td>
<td>Rabbit</td>
<td>0, 28</td>
<td>96</td>
<td>70</td>
<td>0.564</td>
<td>(0.37; 0.85)</td>
</tr>
<tr>
<td>BioThrax</td>
<td>NHP</td>
<td>0, 28</td>
<td>39</td>
<td>70</td>
<td>0.294</td>
<td>(0.14; 0.61)</td>
</tr>
<tr>
<td>AV7909</td>
<td>GP</td>
<td>0, 28</td>
<td>200</td>
<td>70</td>
<td>0.063</td>
<td>(0.02; 0.23)</td>
</tr>
<tr>
<td>AV7909</td>
<td>NHP</td>
<td>0, 28</td>
<td>107</td>
<td>70</td>
<td>0.180</td>
<td>(0.12; 0.27)</td>
</tr>
<tr>
<td>AV7909</td>
<td>GP</td>
<td>0, 14</td>
<td>107</td>
<td>28</td>
<td>0.062</td>
<td>(NA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>106</td>
<td>70</td>
<td>0.081</td>
<td>(0.068,0.141)</td>
</tr>
<tr>
<td>AV7909</td>
<td>NHP</td>
<td>0, 14</td>
<td>64</td>
<td>28</td>
<td>0.151</td>
<td>(0.116, 0.587)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64</td>
<td>70</td>
<td>0.262</td>
<td>(0.17; 24.34)</td>
</tr>
</tbody>
</table>

### Phase 3 Endpoints
- Co-Primary
- Co-Primary
- Secondary
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
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 NF50 ≥ 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)
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 NF50 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 NF50 ≥ 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 NF50 ≥ 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 NF50 ≥ 0.29 and the proportion of BioThrax vaccine participants with a TNA NF50 ≥ 0.29 being greater than -15%.
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$_{50} \geq 0.15$ 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
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
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)
Primary Endpoints

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

Pharmacokinetics and Immunogenicity:

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