Application of a Seamless Phase II/III, Group-Sequential Design in the Development of a *S. aureus* Vaccine

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Staphylococcus aureus Infections

- ***S. aureus*** **can cause serious disease with infections that range from localized skin infections to septic shock**
- **Methicillin resistant *S. aureus* (MRSA) is a major cause of hospital-acquired staphylococcal diseases**
- **Postoperative *S. aureus* infections cause substantial morbidity & mortality**
- **Urgent need to reduce rates of *S. aureus* infection following invasive surgeries**

Merck Candidate *S. aureus* Vaccine (V710)

- **Iron Surface Determinant B (IsdB) Antigen of *S. aureus***
  - expressed and highly conserved in all *S. aureus* strains tested
  - immunogenic during acute *S. aureus* infections
- **V710 vaccine**
  - protective in 3 different murine models
  - well tolerated and immunogenic in Phase I studies
- **Awarded fast-track designation by FDA due to unmet medical need**

GOAL: Accelerate Phase II/III Development

- **Find the "right" population for POC**
  - Risk of *S. aureus* is "high enough" to study quickly
  - Risk window is aligned with Phase I immunogenicity data
- **Reduce "white space" between Phase IIb POC and Phase III pivotal efficacy study**
  - Minimize time between Phases
  - Ability to assess early futility and/or success

Population:
Patients Undergoing Cardiothoracic (CT) Surgery

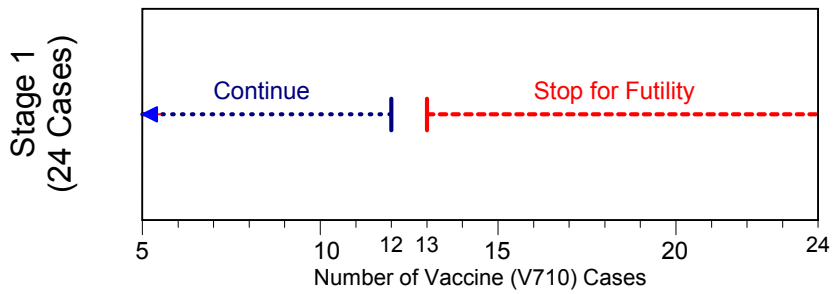
- **Timing of *S. aureus* infections**
  - Risk of *S. aureus* infection (>70%) is highest in first 30 days following CT surgery, and most infections occur in first 90 days
  - Phase I immunogenicity data supported this timeframe
- **Acquisition of patients for clinical trial**
  - Patients usually identifiable at time of CT surgery
  - Serious *S. aureus* infections more frequent (~1-2%) following CT surgery than any other type of surgery (i.e., orthopedic, neurological, or GI surgery)
- **Risk of infection could be different within the context of a clinical trial**

Reduce "White Space": Seamless Phase II/III Study

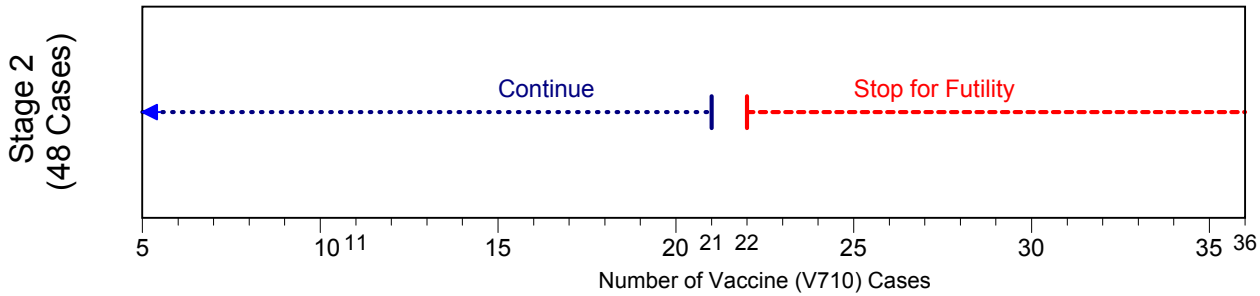
- **Combine POC Phase IIb trial with Phase III efficacy trial to reduce development timelines.**
  - Reduce overall sample size by combining data from both stages in the final analysis.
  - Allow for early stopping for no efficacy or for super efficacy
  - Align an interim analysis with the POC definition to trigger Phase III spending
- **Utilize a "fixed event" design to mitigate the risk of an unexpectedly lower placebo rate**
  - Conditional on the total number of *S. aureus* cases, the number of cases in the vaccine group is binomially distributed
- **Employ exact group sequential methods for binomial data to adjust for multiple interim analyses**

Group Sequential Design

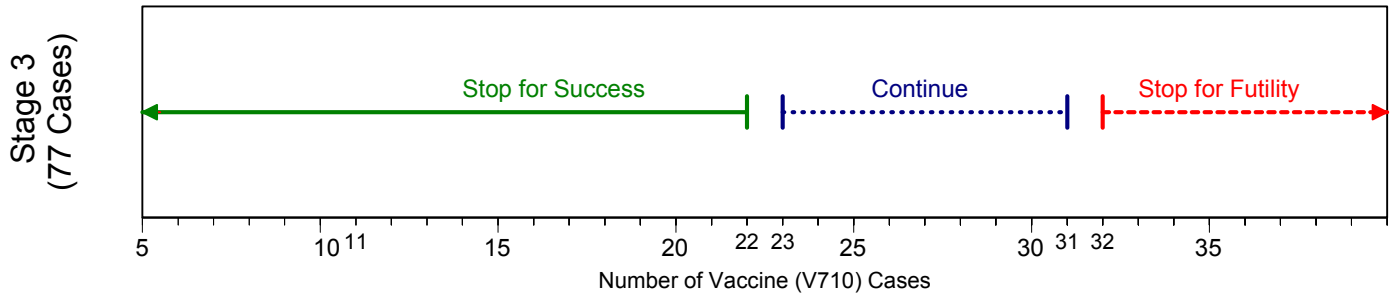
Expected Enrollment



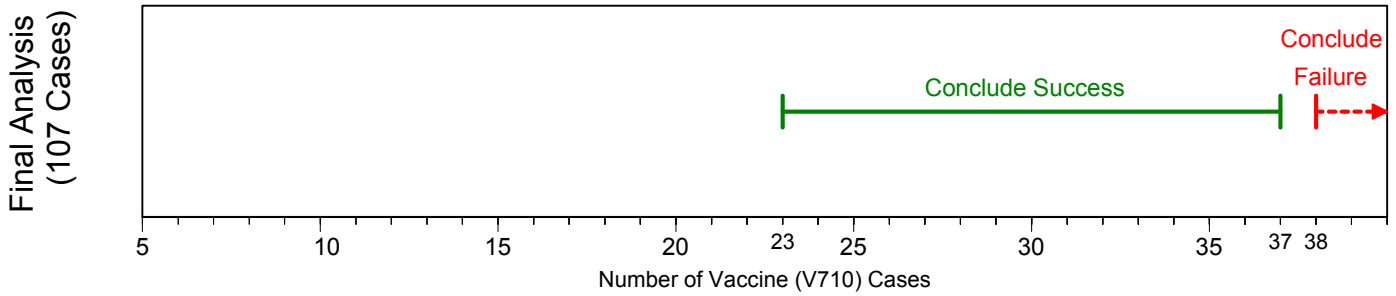
1,800 Subjects



3,600 Subjects



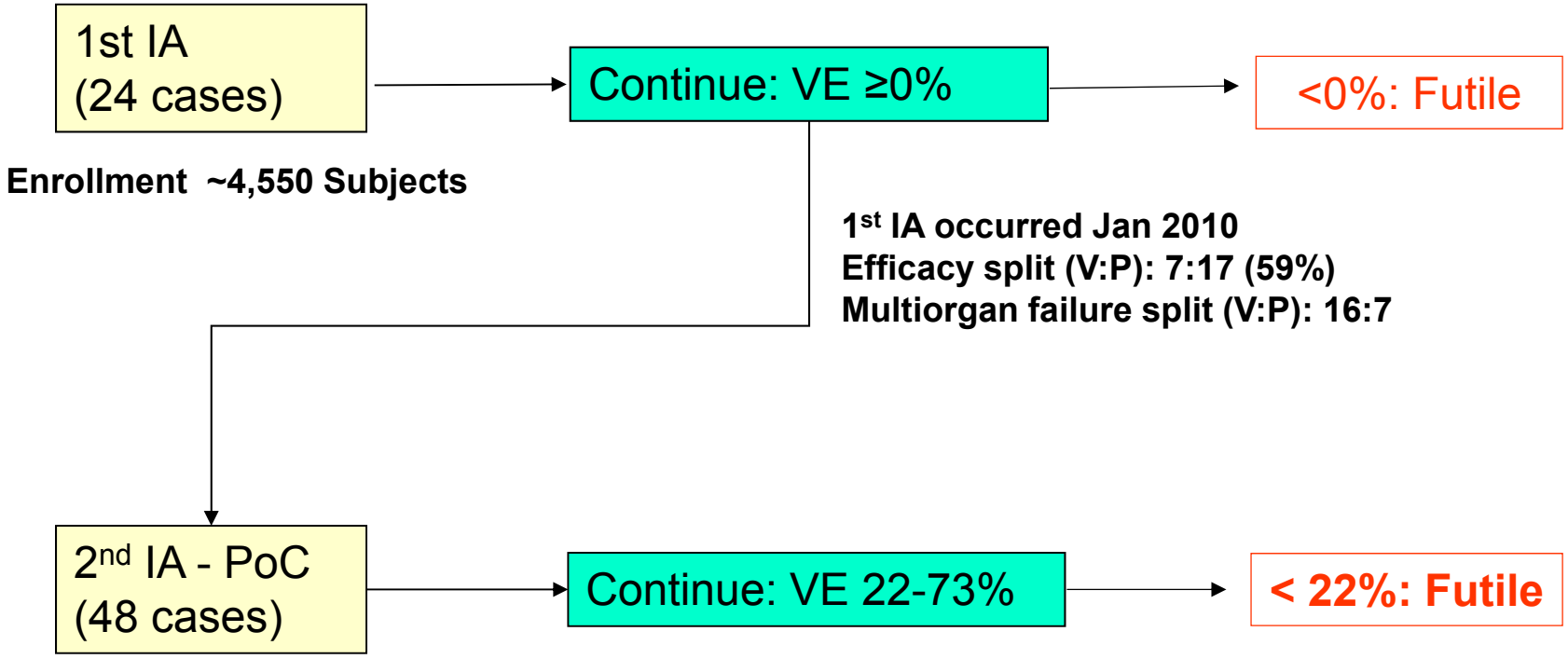
5,800 Subjects



8,050 Subjects

Enrollment Assumptions: VE = 60%; Pbo Rate = 2%; Non-evaluability = 5%; 1:1 randomization

Interim Analysis Results



Enrollment halted due to low efficacy and potential safety issue. After further investigations the study was terminated.

IA = interim analysis
VE=Vaccine efficacy

Analysis of *S. aureus* endpoints

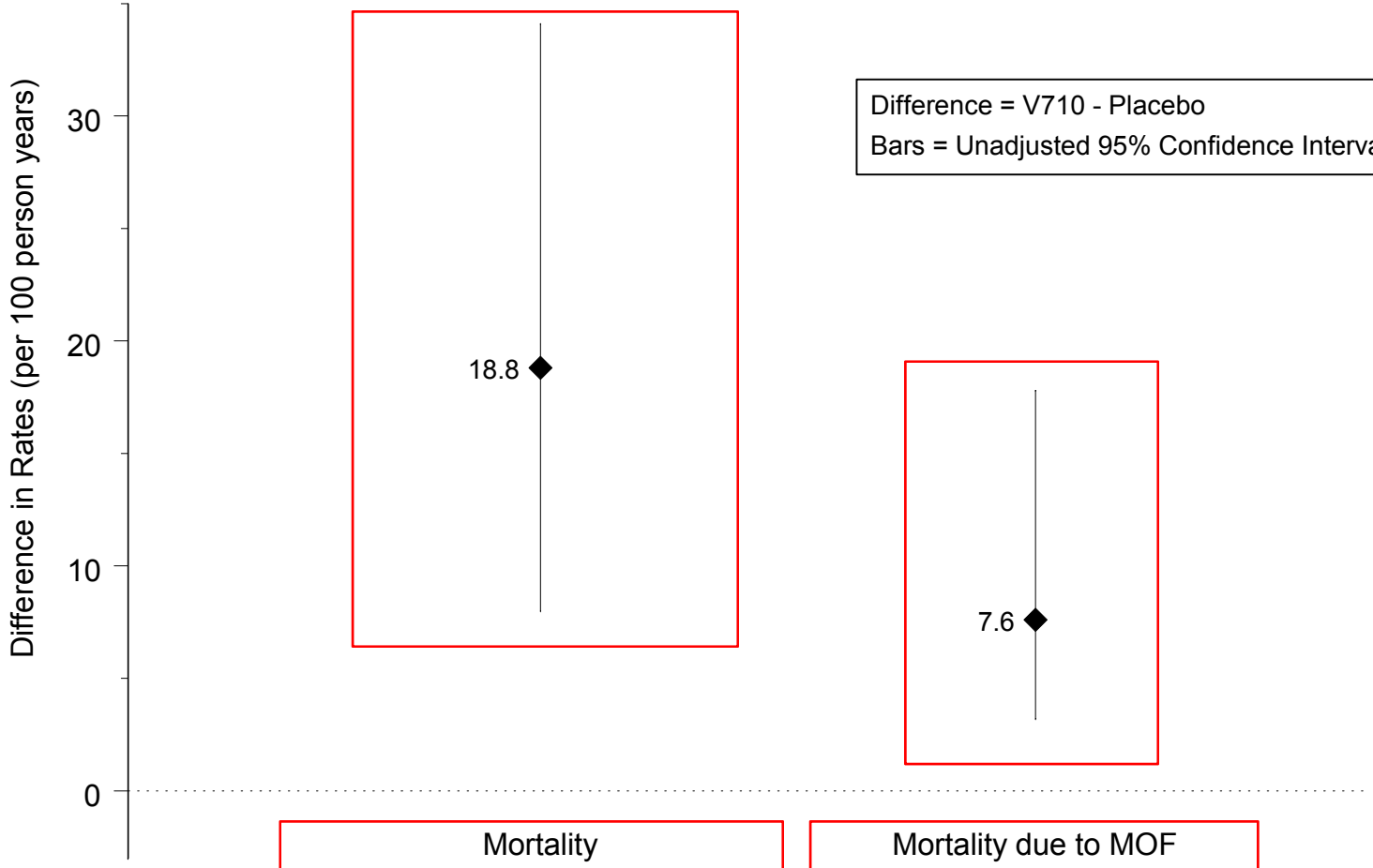
	V710 60mcg	Placebo	Vaccine Efficacy (%) (95% CI)	p-Value (one-sided)
Number of Subjects Randomized	4005	4005		
Number of Subjects Randomized and Vaccinated	3981	3982		
Number of Subjects included in the full analysis set (FAS) population	3528	3517		
Primary Hypothesis				
Number of *S. aureus* Bacteremia and/or DSWI infections	22	27	18.5 (-48.6, 55.8)	0.584
Secondary Hypotheses				
Number of invasive *S. aureus* infections	27	31	12.9 (-50.8, 50.0)	0.347
Number of *S. aureus* surgical-site infections	53	75	29.3 (-1.8, 51.2)	0.032
Exploratory Hypothesis				
Number of *S. aureus* infections (Any)	68	91	25.3 (-3.4, 46.2)	0.040

Safety Analysis – Duration of Study

	V710 60mcg			Placebo			V710 60mcg - Placebo	
	n	Total Follow-Up Time (Pers-Yrs)	Est. Rate (per 100-Pers-Yrs)	n	Total Follow-Up Time (Pers-Yrs)	Est. Rate (per 100-Pers-Yrs)	Estimated Rate Difference (95% CI)	p- value
Subjects in population with follow-up	3958			3967				
with serious adverse events	291	3468.9	8.4	274	3493.4	7.8	0.5 (-0.8, 1.9)	0.424
with serious adverse events involving the diagnosis of *S. aureus*	49	3523.0	1.4	57	3535.2	1.6	-0.2 (-0.8, 0.4)	0.448
with serious vaccine-related adverse events	1	3552.6	0.0	1	3571.6	0.0	0.0 (-0.1, 0.1)	0.997
who died	201	3550.3	5.7	177	3567.9	5.0	0.7 (-0.4, 1.8)	0.200
with multi-organ failure	31	3553.1	0.87	17	3571.4	0.48	0.40 (0.02, 0.81)	0.042

n = Number of subjects with at least one event during the study.
Estimated Rate (per 100-Person-Years) = (n/Person-Years)x100
CI = Confidence Interval

Analysis of Mortality and Multi-Organ Failure in Subjects with *S. aureus* Infections



	Any S. Aureus Infection	Mortality			Mortality due to MOF		
		Deaths	Follow-Up Time (yrs)	Rate (per 100 person-yrs)	MOFs	Follow-Up Time (yrs)	Rate (per 100 person-yrs)
V710	73	15	65.2	23.0	5	65.9	7.6
Placebo	96	4	94.4	4.2	0	94.5	0.0

MERCK Vaccine R&D

MERCK

Conclusions

- **V710 was not efficacious in preventing *S. aureus* bacteremia and/or deep sternal wound infection**
- **Overall mortality rates were not significantly different for vaccine and placebo recipients**
- **V710 appeared to be associated with multiorgan failure**
- **V710 recipients who developed *S. aureus* infection were more likely to die than placebo recipients who developed *S. aureus* infection**
  - based on posthoc analyses; biological basis unknown

Conclusions

- **However, the seamless Phase II/III group-sequential design was successful**
  - The futility and safety assessments prevented the study from continuing further
  - If the vaccine was efficacious, the design would have appropriately accounted for the multiple interim analyses, while ensuring the power was adequate for the desired statistical criterion.

References

- **Fowler VG, Allen KB, *et al*. Effect of an Investigational Vaccine for Preventing *Staphylococcus aureus* Infections After Cardiothoracic Surgery: A Randomized Trial. JAMA. 2013;309(13):1368-1378.**
- **Jennison C and Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton: Chapman and Hall/CRC 2000.**

Backups

Seamless Design: Challenges

- **Logistics of Trial**
  - Internal resource planning:
    - Event-driven – when will interim analyses be reached?
    - When to declare POC? Requiring the same statistical criterion for a stand along Phase IIb POC trial not feasible.
  - Must have final formulation for start of seamless trial
  - Adjudication committee for adjudicating cases
  - DMC for monitoring safety and making decisions at interim analyses
  - Unblinded individuals needed for performing the interim analysis

Seamless Design: Challenges

- **Regulatory Interactions**
  - Acceptance of a combined Phase IIb and Phase III trial for new vaccine
  - Agreement on the statistical criterion needed for showing vaccine efficacy
  - Acceptance on potential for stopping early for success
    - Stopping early? Make sure you are **clearly** above the statistical criterion
    - Boundaries at interim analyses chosen to meet statistical criterion, but would safety database be sufficient in size?
    - Even if statistical criterion is met early, still need to collect sufficient safety follow-up.
  - Even more critical to maintain internal blinding