Development of Merck's *S. aureus* Vaccine (V710)

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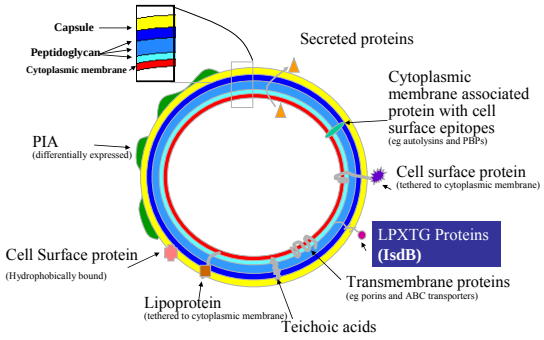
Agenda

- **Introduction**
- V710 Phase I Program
- V710 Phase II/III Efficacy Study (Acute Risk)
- Statistical Considerations in Group Sequential Vaccine Efficacy Studies

Vaccine Target Antigens for *S. aureus*



IsdB Polypeptide as a Vaccine Antigen

- **IsdB represents excellent vaccine candidate**
  - Identified in Intercell's proprietary antigen identification program
  - Cell surface expression makes it accessible to bactericidal antibodies (suspected involvement in iron scavenging)
  - Reactivity confirmed in repeated immunological screens of human serum
  - Protein expressed in all tested *S. aureus* isolates
  - Well conserved in isolates from diverse clinical and taxonomic backgrounds or with differing resistance patterns (including MRSA and VISA)
  - Vaccine was well tolerated, immunogenic, and protective in pre-clinical animal studies.

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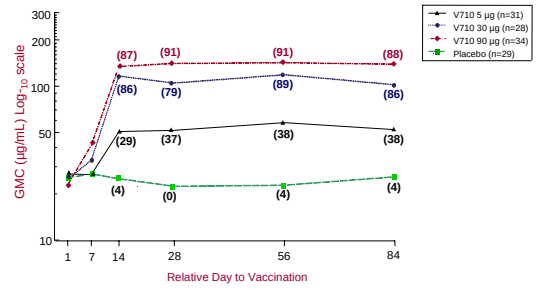
Phase I Program

Protocol 001: Placebo-Controlled, Dose-Ranging Study of 3 Separate V710 Doses in Adults 18-55 Years (n=124)	**Liquid Formulation** (adjuvanted)
↓	
Protocol 002: Comparative Study of Adjuvanted vs. Non-adjuvanted V710 in Adults 18-70 Years (n=64)	**Liquid Formulation** (with and without adjuvant)
↓	
Protocol 004: Placebo-Controlled Study of 60 µg Dose of V710 in Adults 18-80 Years (n=51)	**Lyophilized Formulation** (non-adjuvanted)

Protocol 001:
Immunogenicity Data over Time†



† Immunogenicity based on LUMINEX assay of total IgG against IsdB antigen

% of Subjects with 2-fold rises in IgG concentrations shown in parentheses

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V710 Efficacy Study (P003):
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 supports this timeframe
- **High morbidity of *S. aureus* infections**
  - CT surgery recipients are at high risk for serious *S. aureus* infections
  - Serious *S. aureus* infections carry high attributable mortality
- **Acquisition of patients for clinical trial**
  - Patients usually identifiable at time of CT surgery
  - Serious *S. aureus* infections more frequent (~2%) following CT surgery than any other type of surgery (i.e., orthopedic, neurological, or GI surgery)
- **Generalization to other surgical populations**
  - CT surgery patients often similar to patients undergoing other surgeries with regard to underlying comorbidities and age ranges
  - Similar pathophysiology in the development of postsurgical infections

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V710 Efficacy Study (P003):
Study Design

- **Randomized, double-blind, group sequential, placebo-controlled study**
  - Single-dose of V710 (60 µg) vs. placebo in adults (≥18 years of age) planning to undergo cardiothoracic (CT) surgery using a 1:1 randomization
  - All patients identified, enrolled, and vaccinated at the time surgery is scheduled, provided surgery is anticipated to occur within a 14-60 day timeframe following the time of vaccination
- **Efficacy**
  - Primary: Proportion of patients with serious *S. aureus* infections at any time during the 90-day postoperative period
  - Secondary: Any invasive *S. aureus* infection during the 90-day postoperative period

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- **Statistical Considerations in Group Sequential Vaccine Efficacy Studies**

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Group Sequential Vaccine Efficacy Studies
Statistical Considerations

Efficacy Hypothesis of Interest:

$H_0: V_E = \delta$

$H_1: V_E > \delta$ where,

- $V_E = 1 - RR$ is the vaccine efficacy
- RR is the relative risk of the vaccine compared to placebo
- δ is the prescribed success criterion (e.g., $\delta = .25$ for Gardasil™)

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Group Sequential Vaccine Efficacy Studies: *Exact Conditional Testing Approach*

Let S_v and S_P be the number of cases in the vaccine and placebo groups, respectively.

Assume S_v and S_P are independent Poisson random variables with means λ_v and λ_p .

Then given S_v+S_P, S_v is binomially distributed with parameters S_v+S_P, and $p = \lambda_v/(\lambda_v+\lambda_p)$

- p is the probability that, among the cases, a subject in the vaccine group is a case

Group Sequential Vaccine Efficacy Studies: *Exact Conditional Testing Approach*

Following Chan and Bohidar (1998),

H_0: $V_E = \delta$ versus H_1: $V_E > \delta$ is equivalent to

H_0: $p = p_0$ versus H_1: $p < p_0$

- $p_0=(1-\delta)/(2-\delta)$, when $N_p \approx N_v$ (i.e., 1:1 randomization)

Using this testing approach, the sample size for the study is driven by the number of events needed to be observed.

Group Sequential Vaccine Efficacy Studies: *Exact Conditional Testing Approach*

Total # of Subjects (Cases) Required to Conclude Vaccine Efficacy > δ (~90% power, 2% Placebo Infection Rate, one-sided α = 0.025)

	True VE			
δ	**50%**	**60%**	**70%**	**80%**
0	6668 (95)	4364 (58)	2998 (37)	2106 (24)
0.10	9336 (133)	5640 (75)	3646 (45)	2458 (28)
0.20	14810 (211)	7746 (103)	4618 (57)	2984 (34)
0.25	19932 (284)	9550 (127)	5346 (66)	3336 (38)

δ = success criterion
VE = Vaccine Efficacy

Given the size of the trial, it is desirable to have interim analyses to check for futility or early success.

Group Sequential Vaccine Efficacy Studies: *Group Sequential Tests*

A group sequential K-stage one-sided test of H_0: $p = p_0$ versus H_1: $p < p_0$ can be expressed in terms of the cumulative number of vaccine cases at stage k (S_k) and has the general form (Jennison and Turnbull, 2000):

After group $k = 1,\ldots,K-1$

if $S_k \geq b_k$	stop, accept H_0
if $S_k \leq a_k$	stop, reject H_0
otherwise	continue to stage $k+1$,

after group K

if $S_K \geq b_K$	stop, accept H_0
if $S_K \leq a_K$	stop, reject H_0,

where a_k and b_k, $k=1,\ldots,K$, are the success and futility boundaries, respectively, at the k^{th} stage.

Group Sequential Vaccine Efficacy Studies: *Designing the Testing Plan*

Jennison and Turnbull (2000) provide recursive formulas for calculating (exact) power, Type I errors, p-values, and confidence intervals at a given stage which account for the previous stages.

The Clinical Team must decide on the timing of the interim analyses (based on the number of cases observed) and the futility/success boundaries.

The Statistician must monitor the impact of these decisions on the power and Type I error for the study.

The discreteness of the Binomial distribution can make things interesting.

Group Sequential Vaccine Efficacy Studies: *Impact of Binomial Discreteness*

Total Number of Cases Required to Conclude Vaccine Efficacy > 0.25 (~90% power, one-sided α = 0.025)

Total # Cases	# Vaccine Cases	95% LB	α - level	Power (%)
65	19	0.281	0.0168	90.5
66	20	0.250	0.0249	93.5
67	20	0.268	0.0199	92.5
68	20	0.285	0.0158	91.4
69	21	0.255	0.0234	94.1

Vaccine Case = maximum number of vaccine cases that would still conclude success
95% LB = Lower bound of 95% CI if maximum number of vaccine cases is observed.

Group Sequential Vaccine Efficacy Studies:
Example Testing Strategy – 25% LB

Stages	Targeted Cases	Observed Vaccine Cases Futility† Failure‡	Observed Vaccine Cases for Success‡	Efficacy = 0%		Efficacy = 25%		Efficacy = 70%		Efficacy = 80%	
				Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)
1	20	≥10		58.81		33.47		0.77		0.06	
2	35	≥15	≤6	85.85	<0.01	59.38	0.12	1.27	27.12	0.08	63.61
3	52	≥19	≤15	98.31	0.02	86.47	0.63	2.65	70.04	0.11	95.86
Final	69	≥22	≤21	99.91	0.09	97.62	2.38	6.51	93.49	0.21	99.79

† Futility corresponds to observed efficacy ≤0% in the vaccine group at Stage 1, observed efficacy ≤25% in the vaccine group at Stage 2, observed efficacy <43% in the vaccine group at Stage 3, and observed efficacy <54% in the vaccine group at the Final analysis.

‡ Success corresponds to observed efficacy >79% in the vaccine group at Stage 2, observed efficacy >66% in the vaccine group at Stage 3, and observed efficacy >56% in the vaccine group at the Final analysis.

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Group Sequential Vaccine Efficacy Studies:
Additional Considerations

Ensure Overall Type I error is maintained even if futility analyses are ignored.

How do you handle situations where more than the planned number of cases are available at a given Stage?

An appropriate estimator for Vaccine Efficacy must be chosen.

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