

ZOSTAVAX™

Zoster Vaccine Live (Oka/Merck)

Vaccines and Related Biological Products
Advisory Committee Meeting
December 15, 2005

Merck Research Laboratories

Medical Need for ZOSTAVAX™

- Herpes zoster (HZ) is common in individuals ≥ 50 years of age
- No medical treatment can prevent HZ
- Acute and chronic HZ pain are debilitating
- Available therapies for HZ pain have limitations

ZOSTAVAX™ Program Hypothesis

- Vaccination with a live, attenuated Oka/Merck varicella-zoster virus (VZV) vaccine will address an important unmet medical need by:
 - Reducing the incidence of HZ
 - Reducing the frequency and/or severity of the complications of HZ, including postherpetic neuralgia (PHN)
 - PHN defined as clinically significant pain present ≥ 90 days after HZ rash onset

ZOSTAVAX™ Product Profile

- Live, attenuated varicella-zoster virus vaccine
 - Same Oka/Merck strain as in VARIVAX®
 - Distinct indications
 - Different target population
- No preservative
- Lyophilized product
- Single subcutaneous dose
- Same excipients as VARIVAX®
- Contains a minimum of 19,400 PFU[†] per dose
 - ~14 times the minimum potency of VARIVAX®

[†] Plaque-forming units.

ZOSTAVAX™ Proposed Indications

- ZOSTAVAX™ is indicated for:
 - Prevention of herpes zoster (shingles)
 - Prevention of postherpetic neuralgia (PHN)
 - Reduction of acute and chronic zoster-associated pain
- ZOSTAVAX™ is indicated for immunization of individuals 50 years of age or older

ZOSTAVAX™ Clinical Program

- 8 ZOSTAVAX™ clinical trials
- Shingles Prevention Study
 - Pivotal, multicenter, randomized, placebo-controlled study enrolling 38,546 subjects
- The studies have demonstrated that ZOSTAVAX™:
 - Is efficacious
 - Prevention of HZ and PHN
 - Reduction of pain burden of illness (BOI) related to HZ
 - Reduction of the duration and severity of pain
 - Reduction of overall risk of activities of daily living (ADL) interference due to HZ
 - Is immunogenic
 - Has an excellent safety profile

Collaborators Associated with the Shingles Prevention Study

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ZOSTAVAX™ Agenda

Introduction

David Gutsch, M.D.
Director, Regulatory Affairs

Epidemiology and the Clinical Development Program

Jeffrey Silber, M.D.
Senior Director, Clinical Research

Concluding Remarks

David Gutsch, M.D.
Director, Regulatory Affairs

Discussion Topics

- Epidemiology of HZ and PHN
- Clinical Development Program
- Shingles Prevention Study
 - Study design
 - Key results
- Immunogenicity
- Safety
- Summary of Clinical Results

HZ Is a Consequence of VZV Reactivation

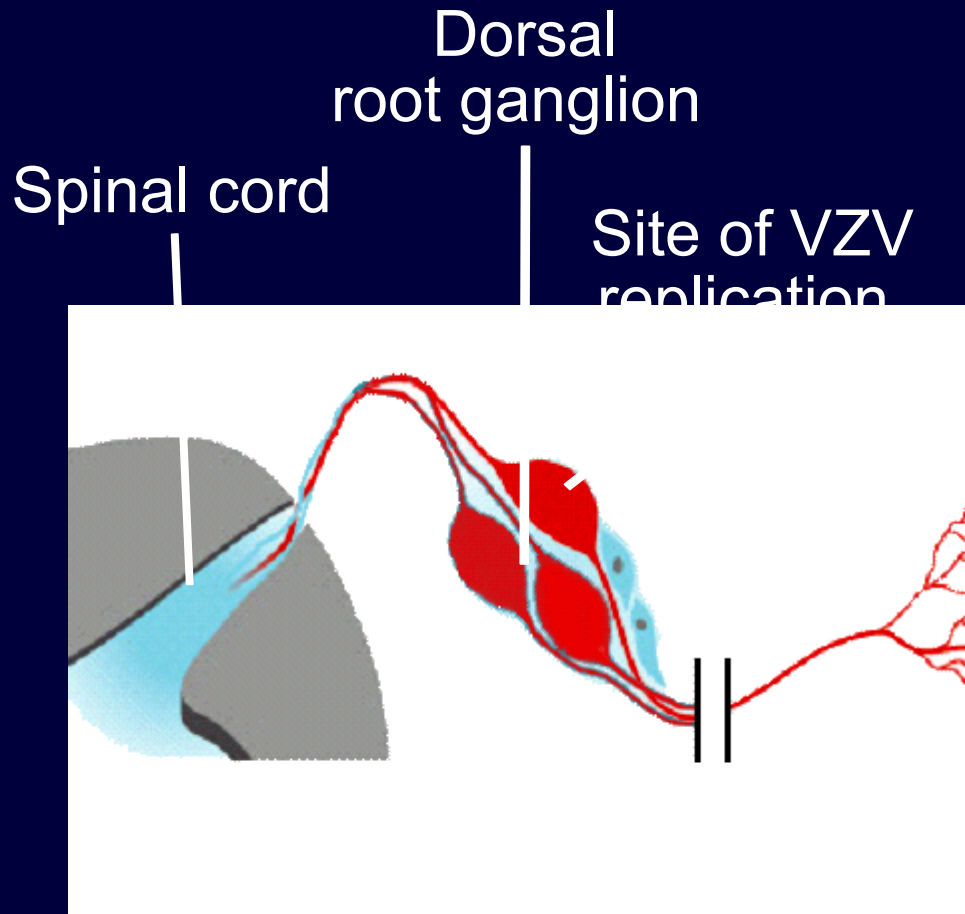


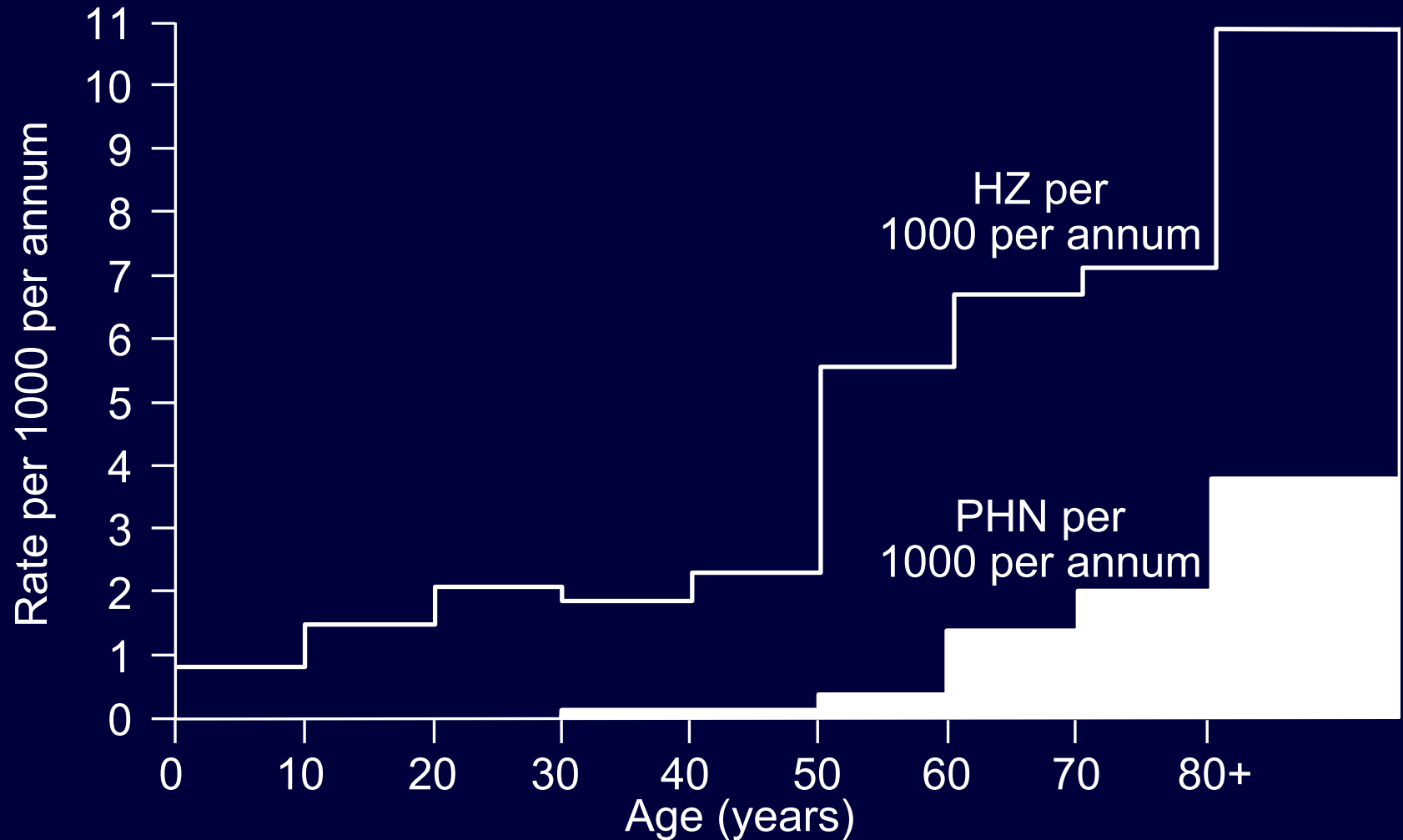
Image courtesy of Courtesy of JW Gnann.

HZ Epidemiology

- An estimated 1 million cases of HZ per year in the US
 - 50,000 to 60,000 hospitalizations
 - 12,000 to 19,000 with primary diagnosis of HZ
 - 70 to 80% of those hospitalized with HZ are immunocompetent
- Lifetime risk of developing HZ ~30%
 - Among people who reach the age of 85 years, up to ~50% will have developed one or more episodes of HZ
- Risk factors for HZ: age, immunosuppression

Epidemiology of HZ/PHN

Occurrence by Age



Hope-Simpson, RE. Postherpetic Neuralgia. *J. Royal College of General Practitioners* 1975; 25:571-5.

Herpes Zoster Incidence*

United States – 2005

Age (Years)	2005 US Population (in Millions) [†]	HZ Cases [‡] (in Thousands)	Percentage of HZ Cases
0 to 19	84	101	10%
20 to 29	41	86	9%
30 to 39	41	82	8%
40 to 49	45	109	11%
50 to 59	37	209	21%
60 to 69	23	158	16%
70 to 79	16	115	12%
≥80	11	117	12%
Total	298	977	100%

* Hope-Simpson, RE. Postherpetic Neuralgia. *J. Royal College of General Practitioners* 1975; 25:571-5.

[†] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat.

[‡] The number of HZ cases was calculated by applying the Hope-Simpson HZ incidence rates to the 2005 US population.

HZ Eruption



Courtesy of Dr. Kenneth Schmader, Duke University and Durham VA Medical Centers.

Ophthalmic Zoster

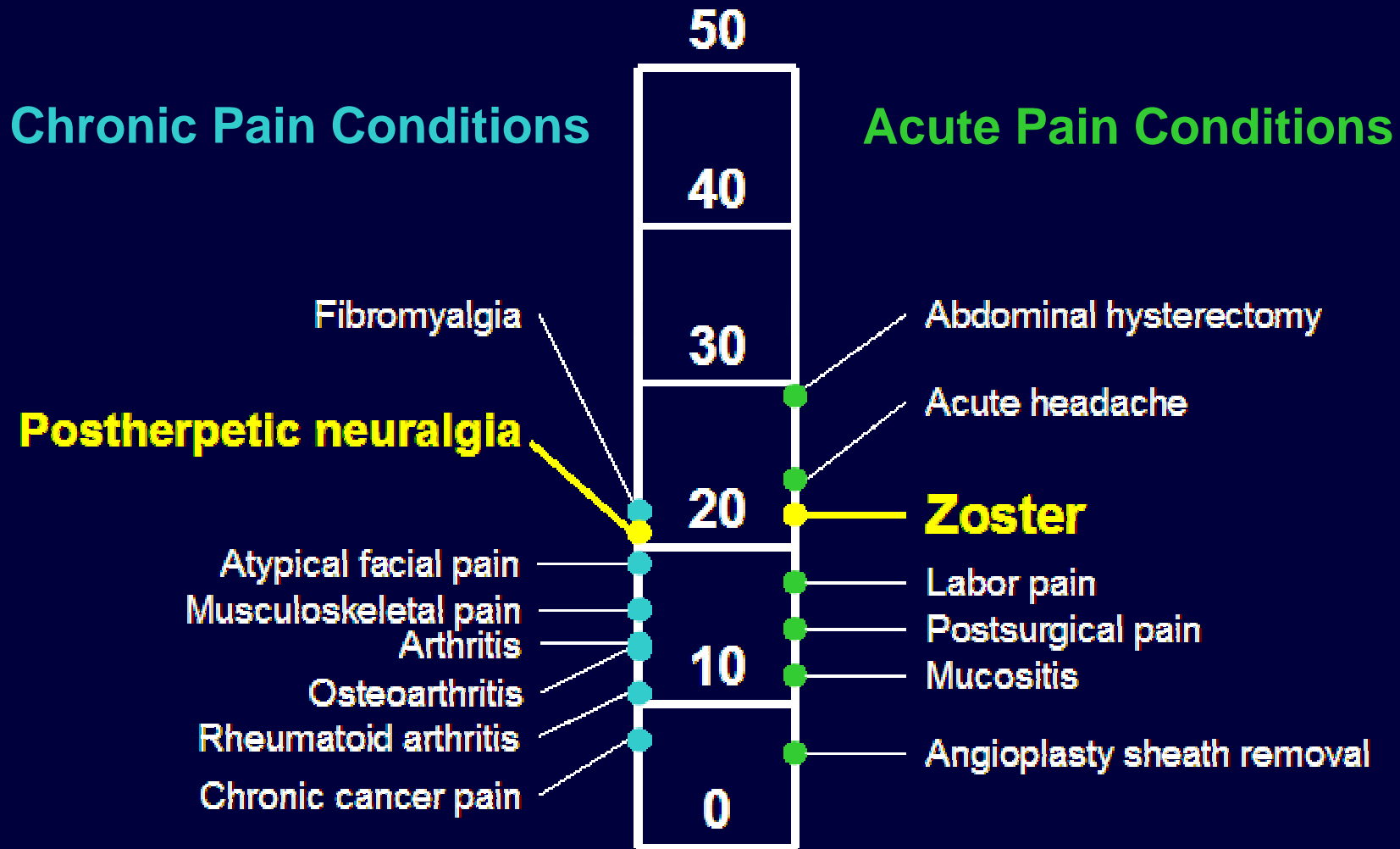


Courtesy of MN Oxman UCSD/San Diego VAMC.

Complications of HZ

- Neurologic
 - Acute neuritic pain (>90%)
 - Postherpetic neuralgia (PHN)
 - Limb weakness
 - Sensory loss
 - Autonomic dysfunction
 - Meningitis
 - Myelitis
 - Encephalitis
- Ocular
 - Visual impairment
- Cutaneous
 - Scarring
 - Bacterial superinfection
- Disseminated disease
 - Mortality rate up to 40%

Comparison of Pain Severity

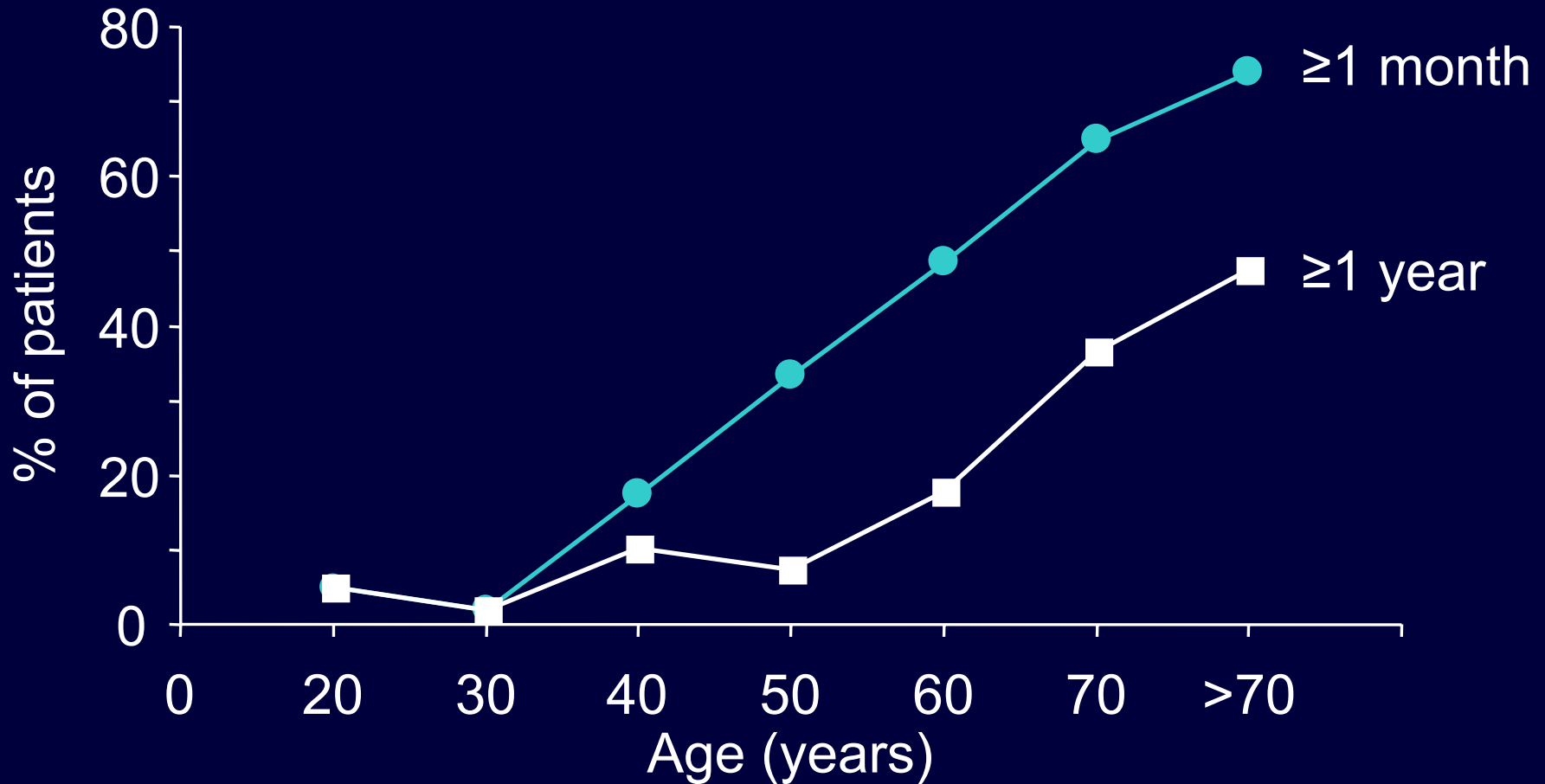


Reprinted from Katz J, Melzack R. Measurements of pain. *Surg Clin N Amer* 1999;79:231-52, with permission from Elsevier.

Postherpetic Neuralgia (PHN)

- Pain in area of the rash that is present after HZ resolution
 - Constant or intermittent
 - Dull and achy or sharp and lancinating
 - Allodynia (exaggerated pain provoked by light touch) often the most troublesome symptom
- 10 to 20% of HZ patients develop PHN
 - Risk increases dramatically with age
 - Impact can be physical, psychological, social, functional
- Can persist for months to years
- Estimated 500,000+ prevalent PHN cases in the US

Percentage of HZ Patients with Persistent Pain



Adapted from DeMoragas JM, Kierland RR. *Arch Dermatol.* 1957;75:193-6.

Medical Need: Limitations of Current Therapies

- For HZ
 - Antivirals (acyclovir, famciclovir, valacyclovir)
 - Reduce severity of acute HZ
 - May shorten duration of PHN
 - Limited effect on PHN incidence
 - Corticosteroids
 - No effect on incidence or severity of PHN
- For PHN
 - Available therapies have limited benefit
 - Side effects can be dose-limiting

Rationale for ZOSTAVAX™ Development

- Risk for HZ and PHN
 - 87,000,000 people in the US are ≥ 50 years of age
- Limitations of current therapies
- No existing intervention can prevent HZ and PHN

Discussion Topics

- Epidemiology of HZ and PHN
- Clinical Development Program
- Shingles Prevention Study
 - Study design
 - Key results
- Immunogenicity
- Safety
- Summary of Clinical Results

Proof of Concept

Using Inactivated Oka/Merck VZV Vaccine

- Redman, et al., *J Infect Dis* (1997) – Bone marrow transplant recipients
 - Reduced incidence of PHN
 - Reduced severity of HZ
- Hata, et al., *NEJM* (2002) – Stem cell transplant recipients
 - Reduced incidence of HZ

Clinical Development Plan

Study Objectives

- Dose selection
 - Establish vaccine potency that is immunogenic and well tolerated
 - ZOSTAVAX™ N=583, Placebo N=91
- Efficacy
 - Determine vaccine impact on incidence of HZ and complications
 - ZOSTAVAX™ N=19,270, Placebo N=19,276
- Two-dose/booster
 - Safety and immunogenicity of a second dose
 - ZOSTAVAX™ N=300, Placebo N=105
- Safety
 - Determine safety profile:
 - VZV-inexperienced - ZOSTAVAX™ N=159, Placebo N=3
 - High potency - ZOSTAVAX™ N=695, Placebo N=0
- TOTAL: ZOSTAVAX™ N=21,007 Placebo N=19,475

Rationale for ZOSTAVAX™ Potency Range

- Potencies evaluated in clinical studies ranged from 2,000 PFU to 207,000 PFU
- Early studies suggested that a single dose of ~17,000 PFU or higher boosts VZV-specific cell-mediated immunity (CMI)
- These data formed the basis for selection of target minimum potency of ~19,000 PFU in the efficacy study

Study Population for ZOSTAVAX™

- ZOSTAVAX™ has been studied in adults 30 to 99 years of age, with a broad variety of underlying medical conditions
- Enrollment by gender

Male	12,051 (57.8%)	Female	8812 (42.2%)
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- Ethnicity of study population

White	19,914 (95.5%)	Native American	37 (0.2%)
Black	412 (2.0%)	Other	73 (0.4%)
Hispanic	298 (1.4%)	Unknown	3 (0.0%)
- With the exception of age-related trends, no differences in efficacy, immunogenicity, or safety by race and gender

Discussion Topics

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Shingles Prevention Study (SPS)

- Double-blind, placebo-controlled, multicenter trial, 22 sites
 - Study timeline: Nov-1998 to Apr-2004
- Dept. of Veteran Affairs Cooperative Studies Program (VA CSP) collaboration with the National Institutes of Health (NIH) and Merck & Co., Inc.
- 38,546 subjects ≥ 60 years of age
 - Age-stratified (60 to 69 years, ≥ 70 years)
 - 90% had one or more underlying medical conditions
- Randomized 1:1 to receive ZOSTAVAX™ or placebo
 - Most doses administered near proposed expiry potency
- Monthly telephone follow-up to identify HZ cases, monitor adverse experiences, and ensure subject retention
- All subjects actively contacted at the end of the study

SPS Study Population

	<u>ZOSTAVAX™</u>	<u>Placebo</u>
Gender:		
Male	11,403 (59.2%)	11,357 (58.9%)
Female	7867 (40.8%)	7919 (41.1%)
Age (in years):		
Mean	69.4	69.4
Range	60 to 99	59 to 94
Race:		
Black	395 (2.0%)	420 (2.2%)
Hispanic	265 (1.4%)	248 (1.3%)
White	18,393 (95.4%)	18,381 (95.4%)
Other	214 (1.1%)	223 (1.2%)

Most Frequently Reported Prior Medical Conditions in SPS

- >20%
 - Arthritis
 - Hypertension
- >10 to 20%
 - Prostate disorder
 - Allergic reaction
 - Gastrointestinal disorder
 - Hypothyroidism
 - Hypercholesterolemia
- >5 to 10%
 - Coronary artery disease
 - Diabetes mellitus
 - Hyperlipidemia
 - Osteoporosis
 - Depression
 - Glaucoma

Most Frequently Reported Prior Medical Conditions in SPS (Cont'd)

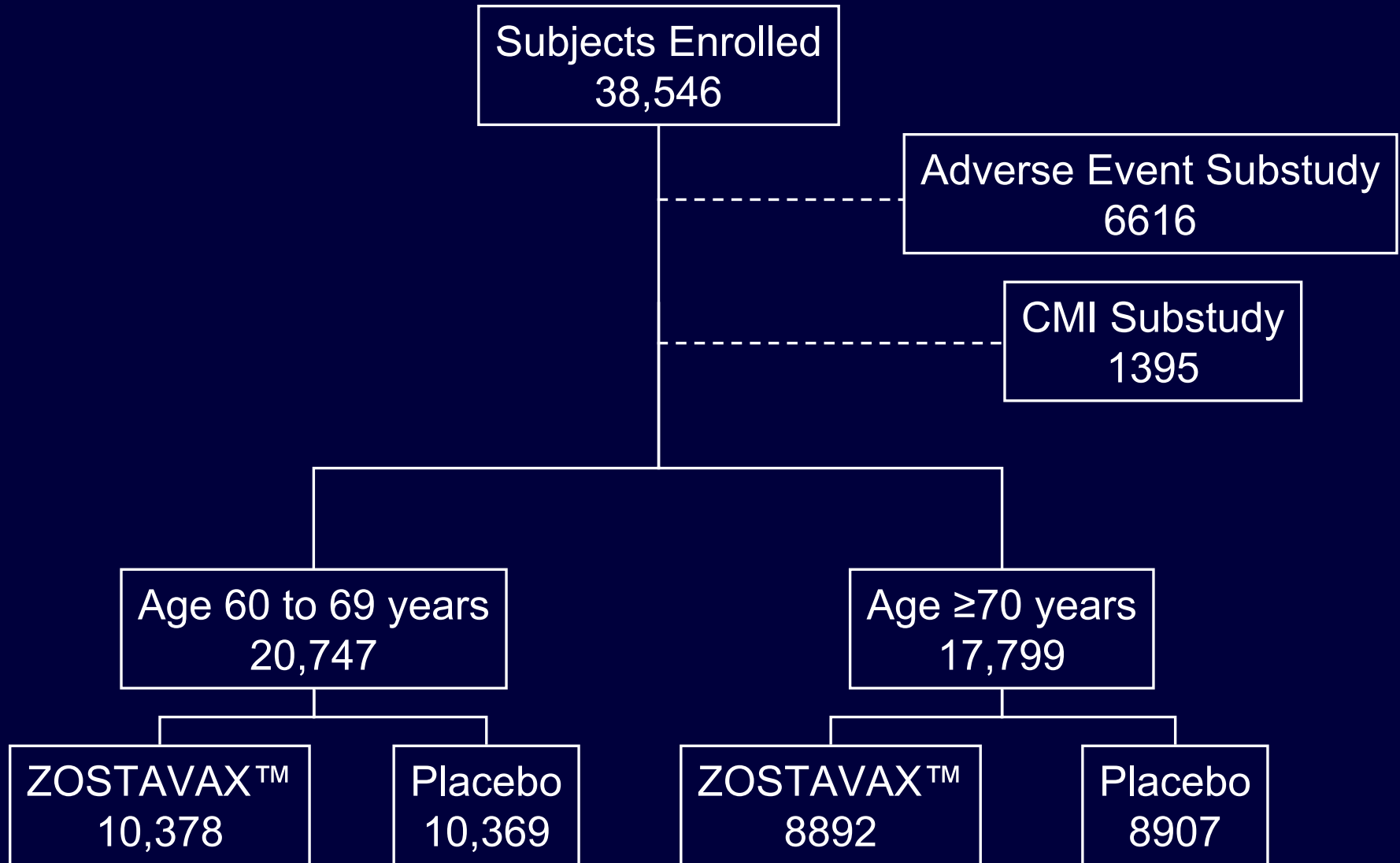
- 1 to 5%

- | | | |
|------------------|----------------------------|------------------------|
| – Carcinoma | – Cerebrovascular accident | – Deafness |
| – Edema | – Insomnia | – Ear disorder |
| – Headache | – Neuropathy | – Eye disorder |
| – Hernia | – Sleep disorder | – Prostate carcinoma |
| – Pain | – Asthma | – Impotence |
| – Back pain | – Emphysema | – Menopause |
| – Colitis | – Lung disorder | – Urinary incontinence |
| – Constipation | – Rhinitis | |
| – Esophagitis | – Sinusitis | |
| – Anemia | – Acne | |
| – Gout | – Skin carcinoma | |
| – Bone disorder | – Psoriasis | |
| – Joint disorder | – Skin disorder | |
| – Anxiety | – Cataract | |

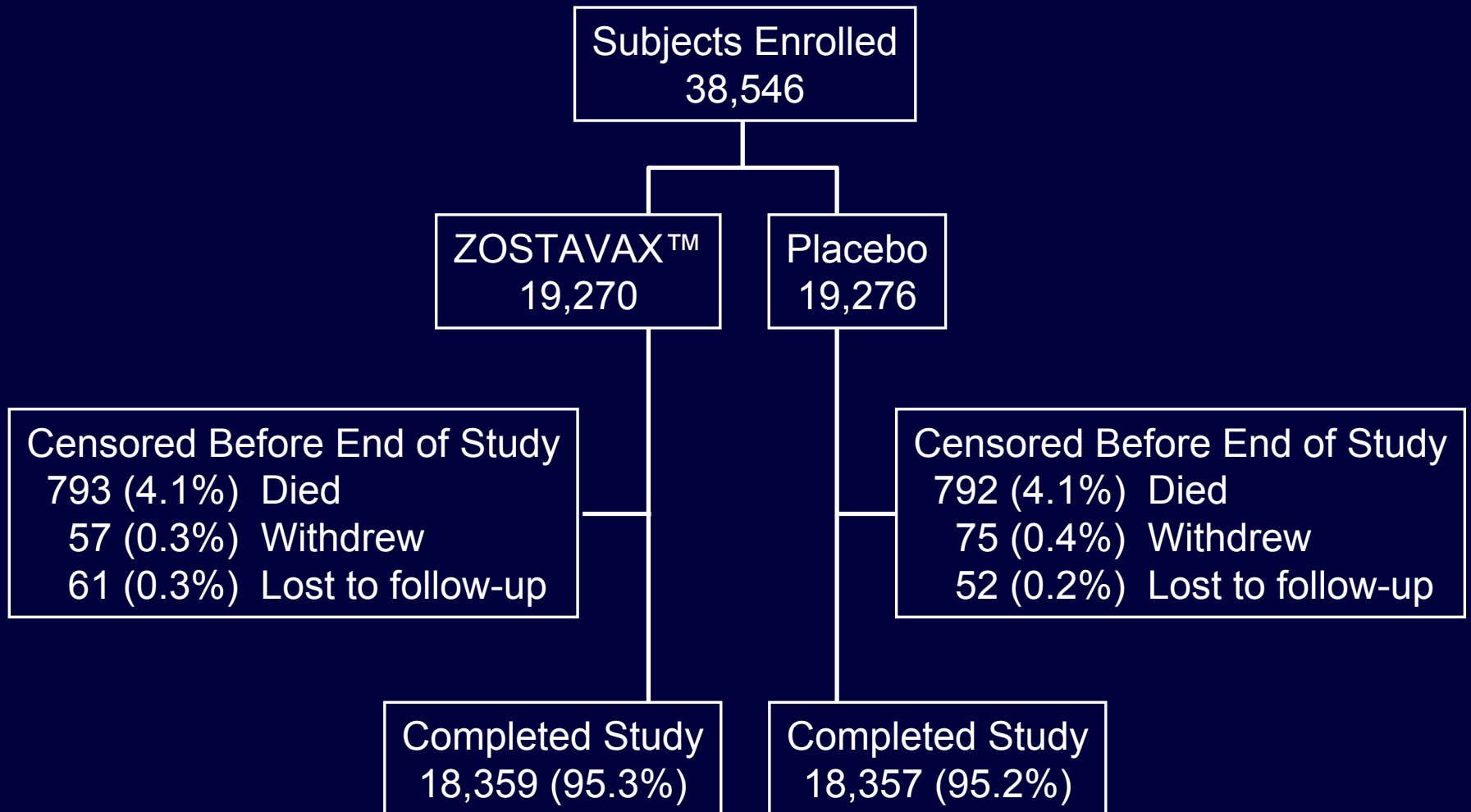
SPS Substudy Design

- Adverse Event Monitoring Substudy (N=6616)
 - Conducted at all 22 study sites
 - Detailed safety assessment
- Cell-mediated Immunity Substudy (N=1395)
 - Conducted at 2 study sites
 - Specimens obtained at baseline and postvaccination (6 weeks; 1, 2, and 3 years)
- Persistence of Efficacy Substudy (N~7500)
 - Conducted at 12 study sites
 - Ongoing follow-up from efficacy study
 - Projected to continue through ~10 years postvaccination

SPS Subject Randomization

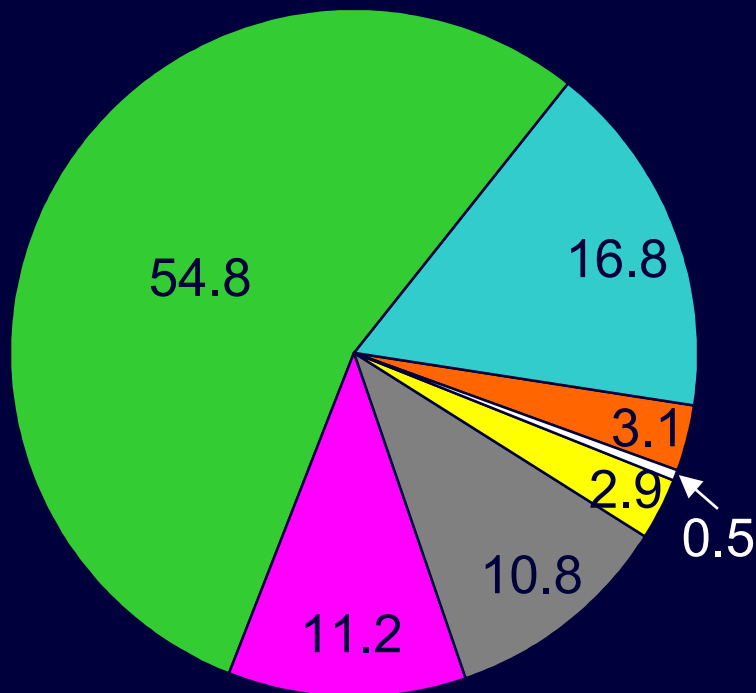


SPS Subject Disposition

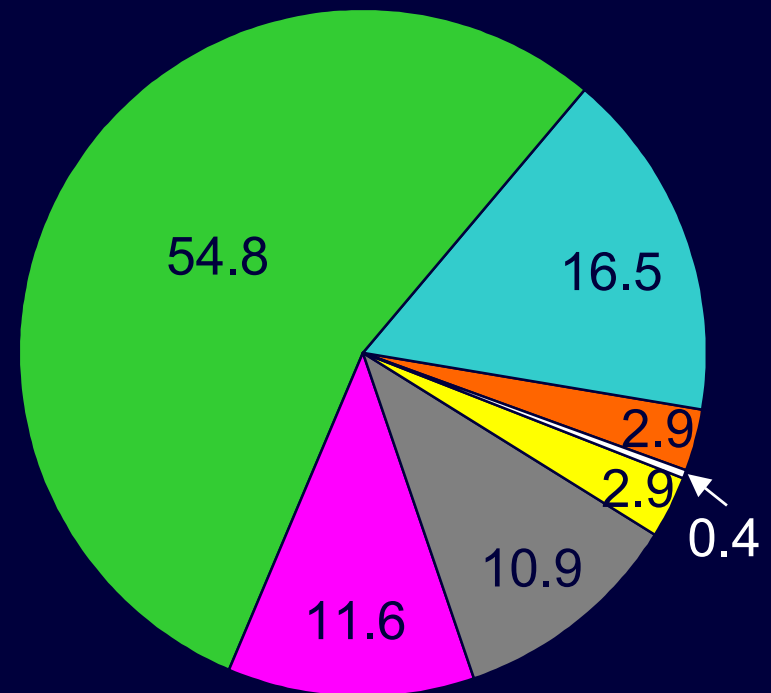


Summary of Day 42 Safety Follow-up (Whole Population in SPS)

ZOSTAVAX™ (N=19,270)
92.8% with contact by Day 60



Placebo (N=19,276)
93.0% with contact by Day 60



- Without safety follow-up
- Vaccination Report Cards
- Subject called ATRS
- Staff called ATRS
- Staff followed up an ATRS fax (Form E)
- Other contacts within 60 days (Form E)
- Contacts for AE (Forms E,F)

Follow-up of Suspected HZ Cases

- Subjects with signs or symptoms suggestive of HZ were asked to report to study site within 24 hours, to initiate 6 months of follow-up
- Study sites conducted the following activities:
 - Performed clinical evaluation
 - Made provisional diagnosis
 - Sampled lesions for PCR (+/- viral culture)
 - Obtained digital photographs of HZ eruption
 - Collected blood samples for immunological testing
 - Administered HZ pain and health-related quality-of-life questionnaires
- Provided treatment for HZ
 - Famciclovir and pain management

Efficacy Endpoints Supporting Label Indications

- Incidence of HZ
- Incidence of PHN
- HZ pain burden of illness (BOI)

Pain was evaluated on a 0-to-10 scale
using a validated questionnaire

Efficacy analyses were based on a
modified intention-to-treat (MITT) population

Rationale for Selection of Endpoints in SPS

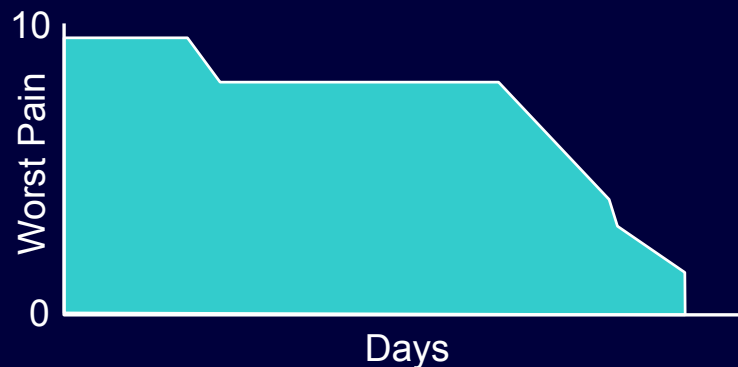
- At initiation of study, existing scientific data suggested vaccination may prevent PHN and ameliorate HZ-associated pain
 - Co-primary endpoints of HZ BOI and PHN were deemed most clinically relevant
 - Tertiary endpoint on incidence of HZ was subsequently elevated to a key secondary endpoint
- Risk of PHN increases after age 60
 - Study enrolled subjects ≥ 60 years of age in order to provide adequate power for PHN endpoint

SPS Efficacy Endpoint Definitions

- Herpes zoster
 - Suspected HZ: 6 months of protocol-specified follow-up
 - All suspected HZ cases were clinically adjudicated according to detailed Standard Operating Procedure
 - Confirmed HZ: Determined by PCR, viral culture, and clinical adjudication
- Postherpetic neuralgia
 - Pain score ≥ 3 beyond 90 days after HZ rash onset

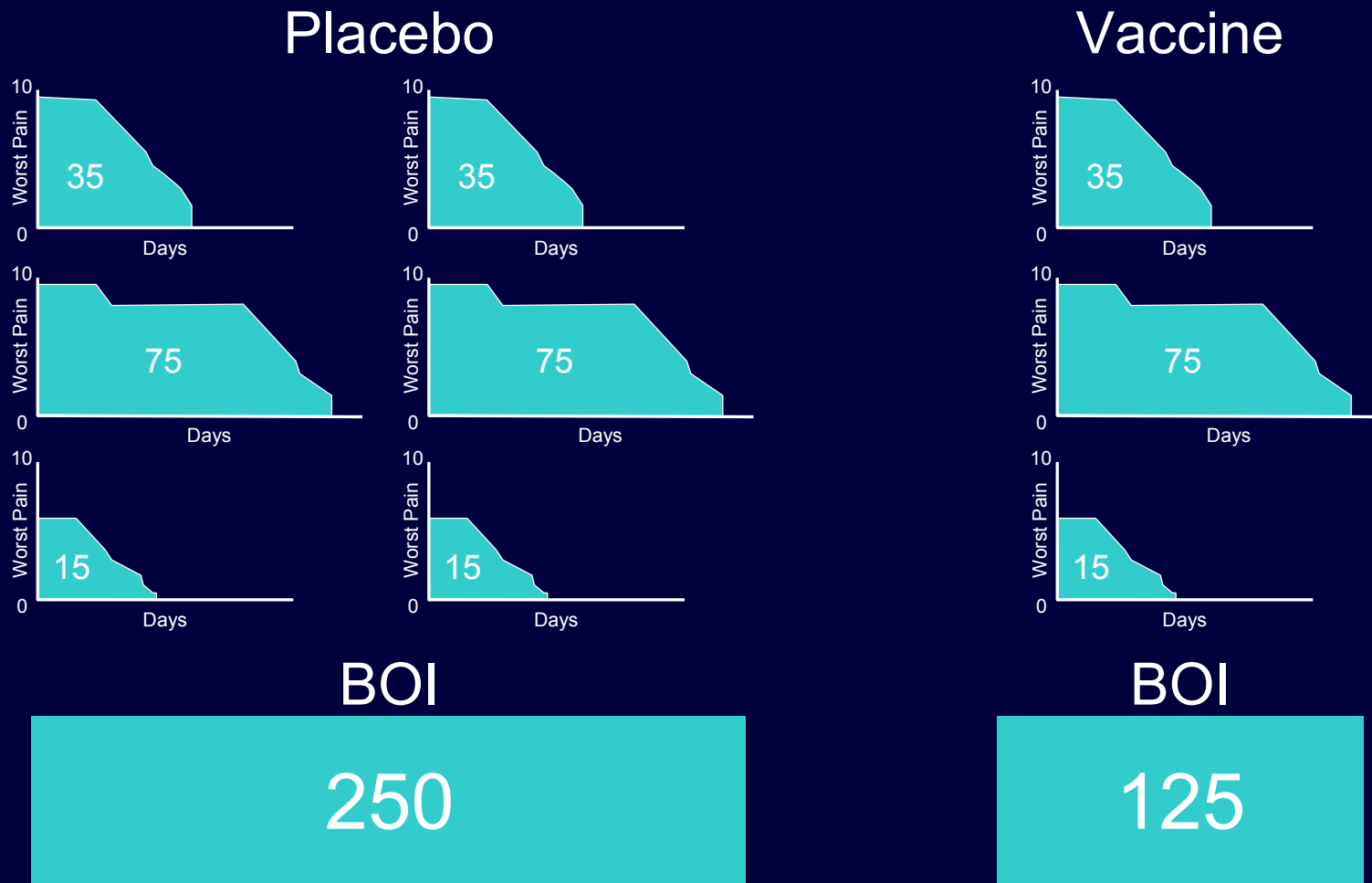
SPS Efficacy Endpoint Definitions

- HZ pain burden of illness (BOI)
 - Population measure
 - Sensitive to the incidence, duration and severity of HZ pain over 6 months



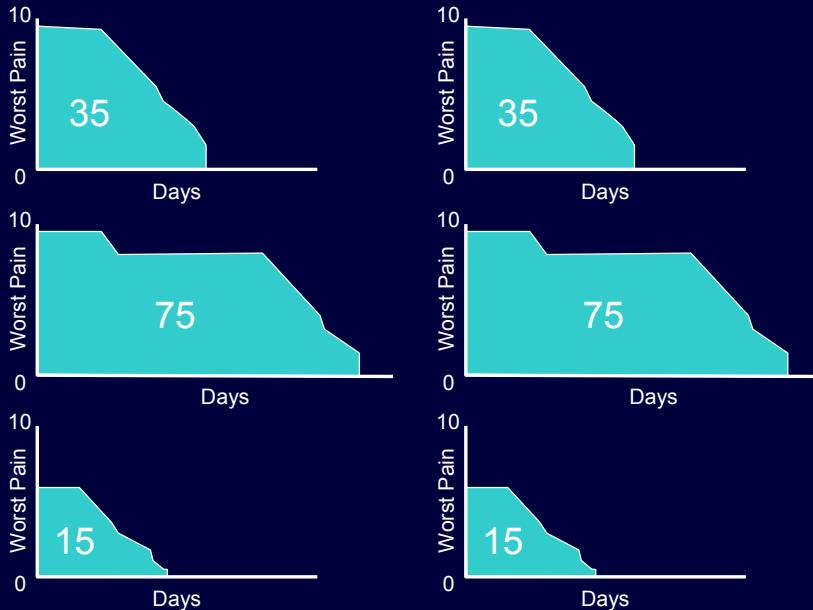
- Primary analysis was performed on entire efficacy (MITT) population
 - Severity-by-duration (AUC) calculated for each HZ case
 - Subjects without HZ were assumed to have no HZ-associated pain (i.e., AUC=0)

Hypothetical Example of HZ BOI: Reduction in HZ Incidence but Not Severity



Hypothetical Example of HZ BOI: Reduction in HZ Severity but Not Incidence

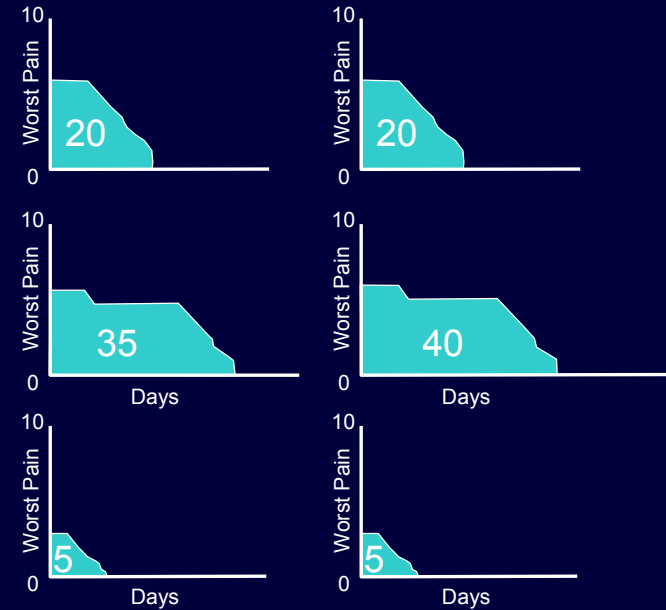
Placebo



BOI

250

Vaccine

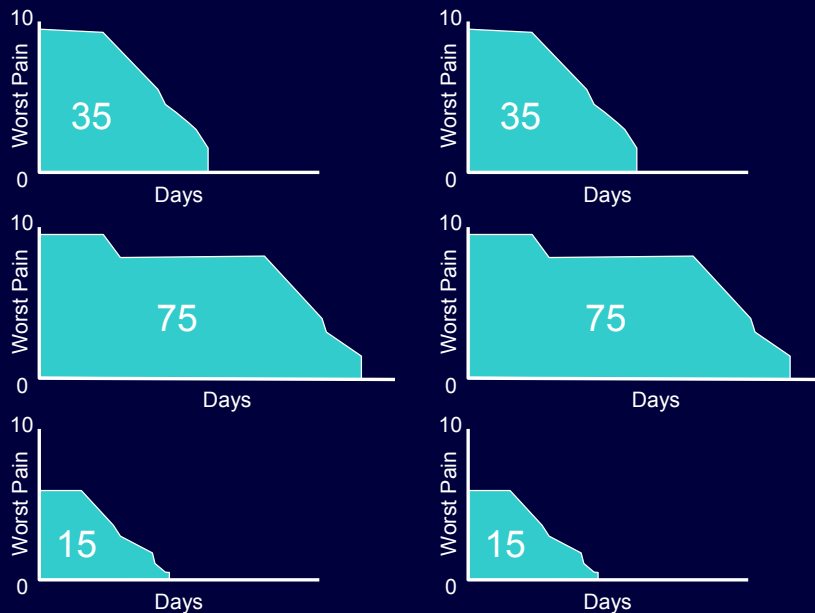


BOI

125

Hypothetical Example of HZ: Reduction in Both Incidence and Severity of HZ

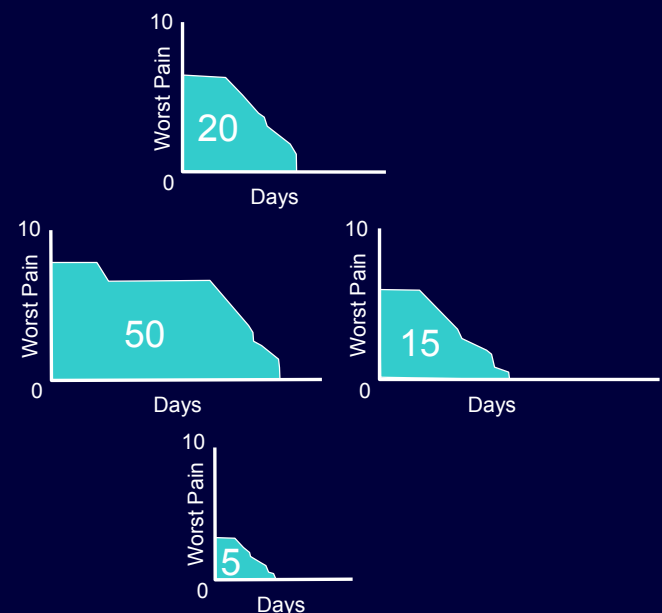
Placebo



BOI

250

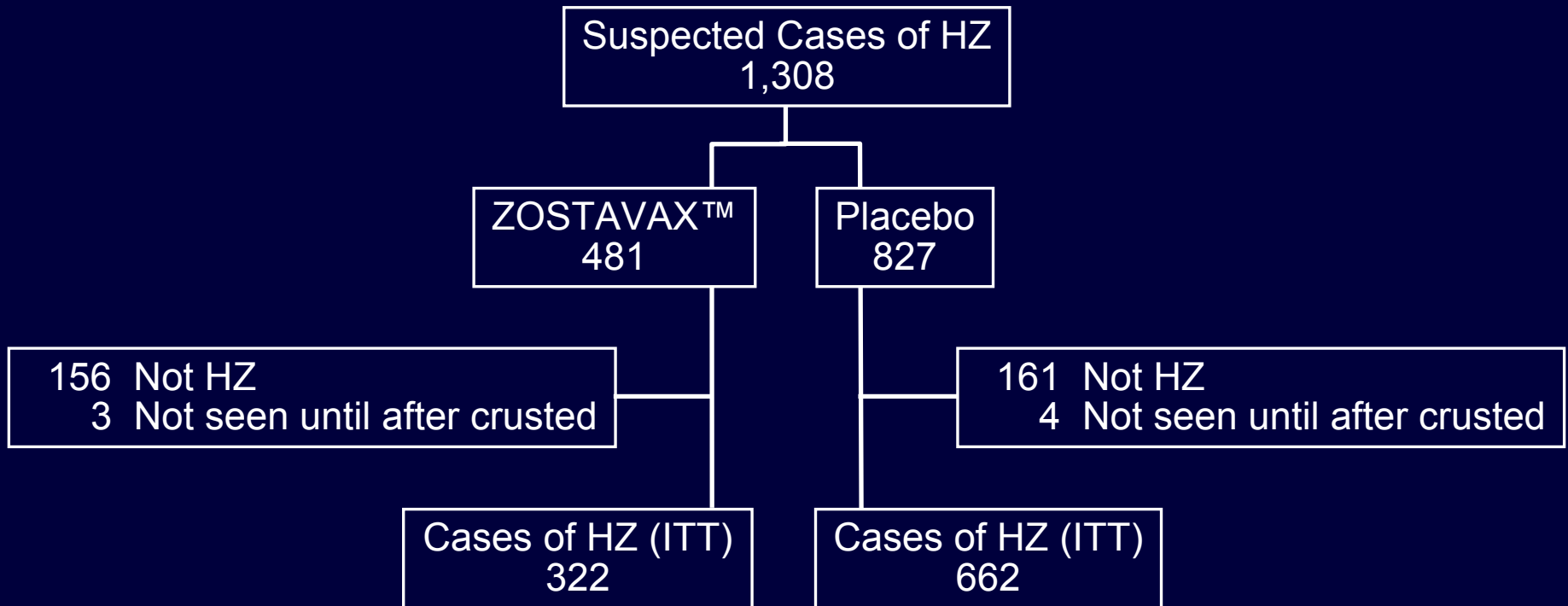
Vaccine



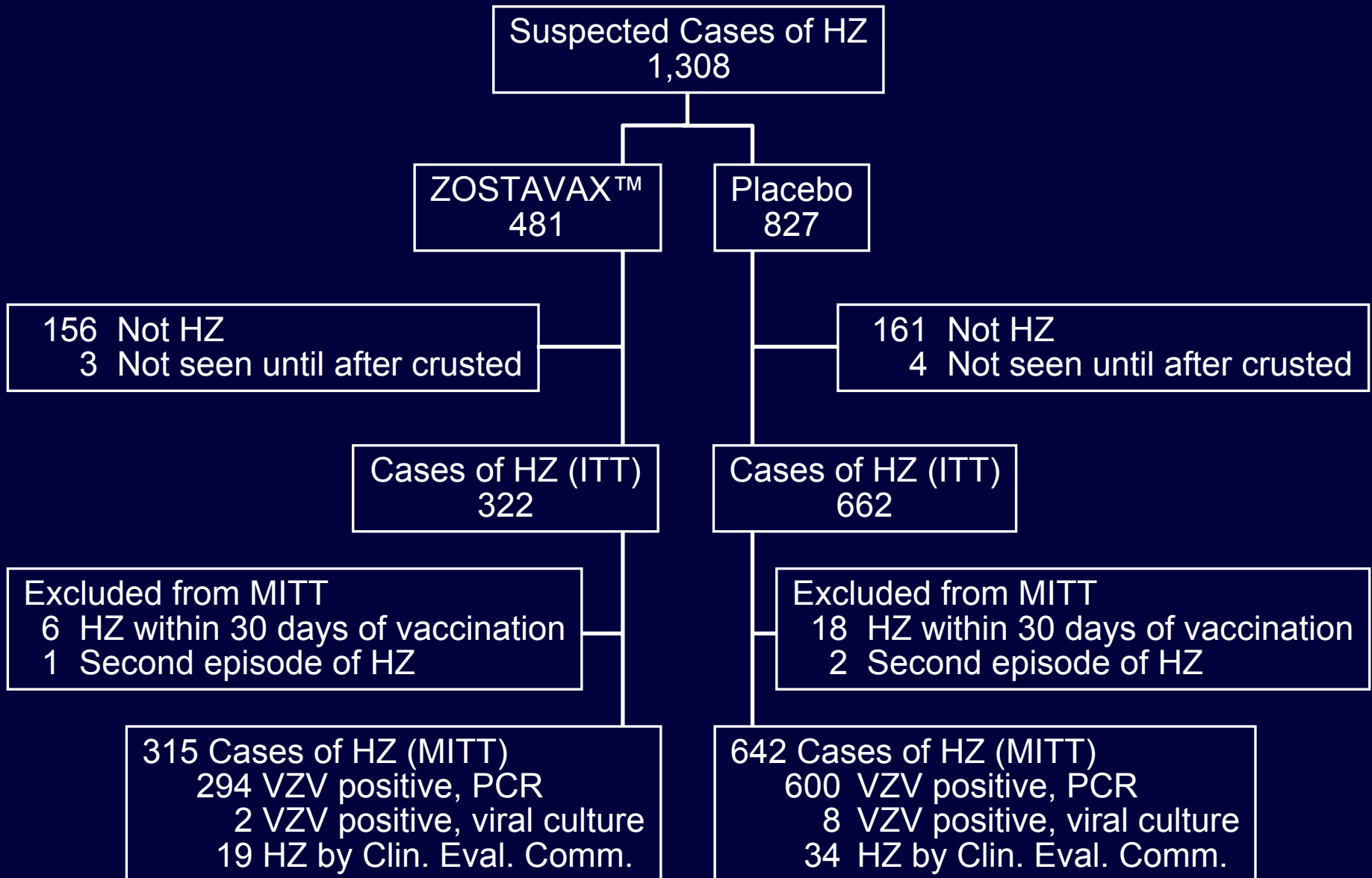
BOI

90

SPS Efficacy Population

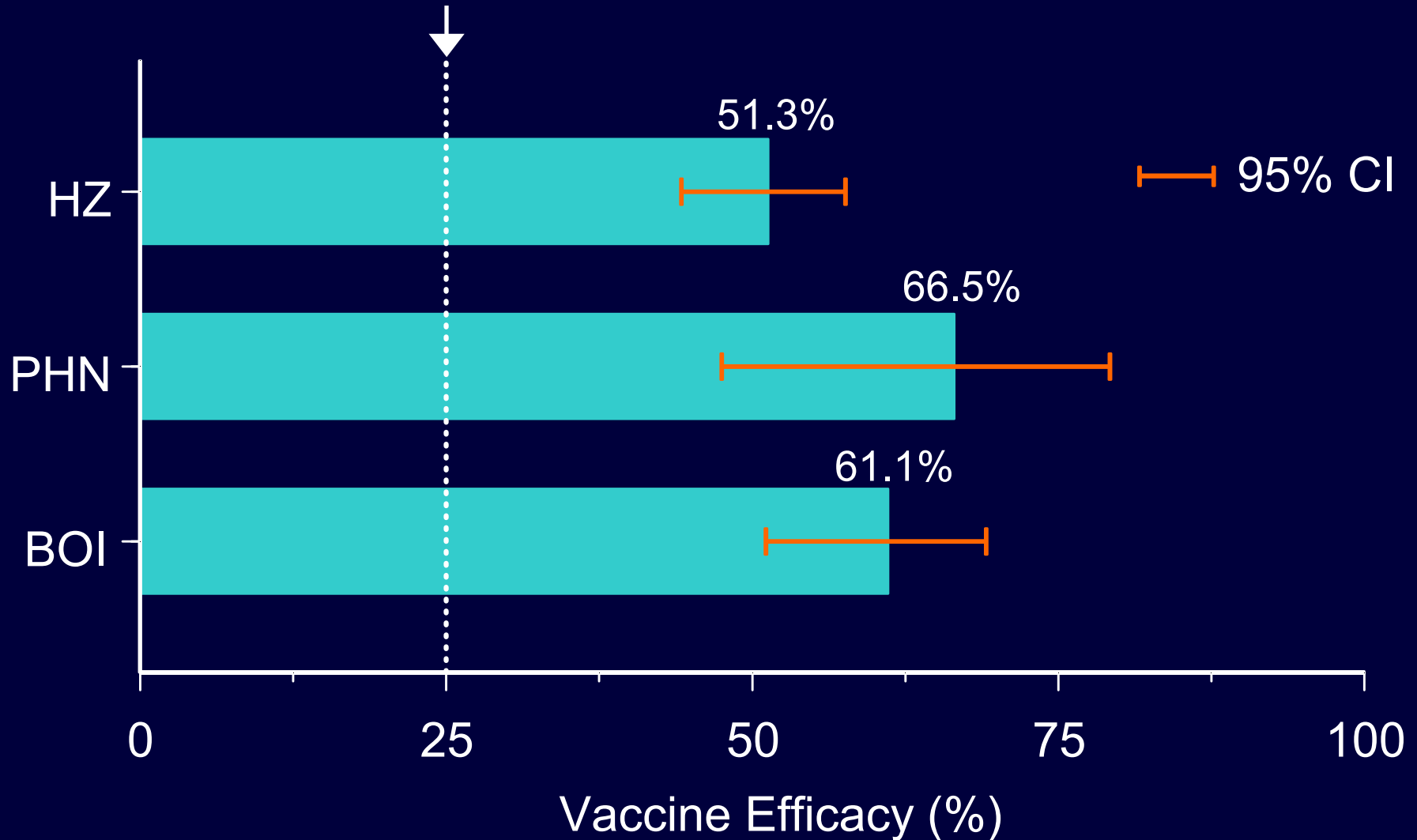


SPS Efficacy Population



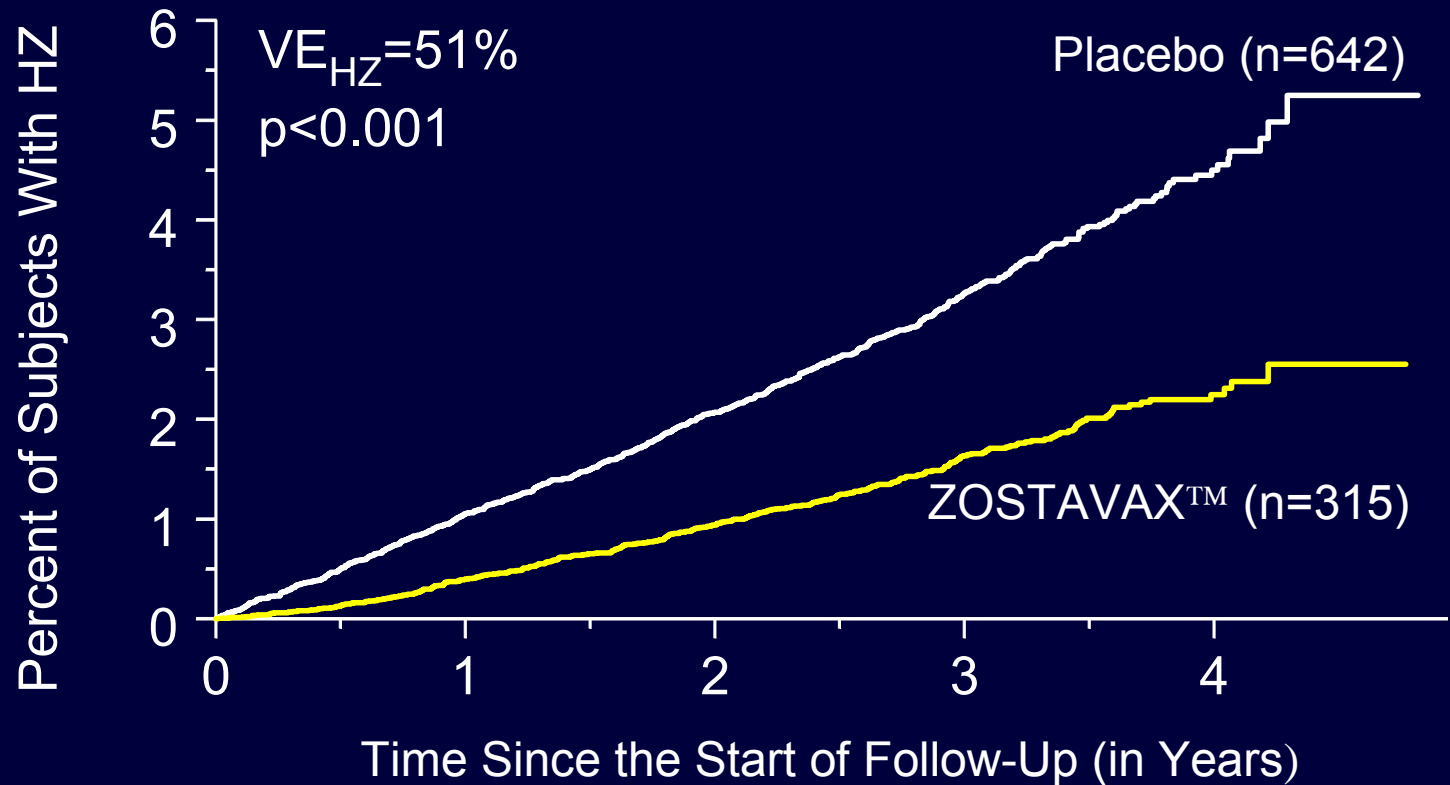
ZOSTAVAX™ Efficacy

25%=prespecified lower
bound success criterion



ZOSTAVAX™ Efficacy: HZ Incidence

Estimate of the Cumulative Incidence of HZ Over Time by Vaccination Group (MITT Population)



Number of subjects at risk

ZOSTAVAX™	19254	18994	18626	9942	1906
Placebo	19247	18915	18422	9806	1856

Rate of HZ Complication (MITT Population)

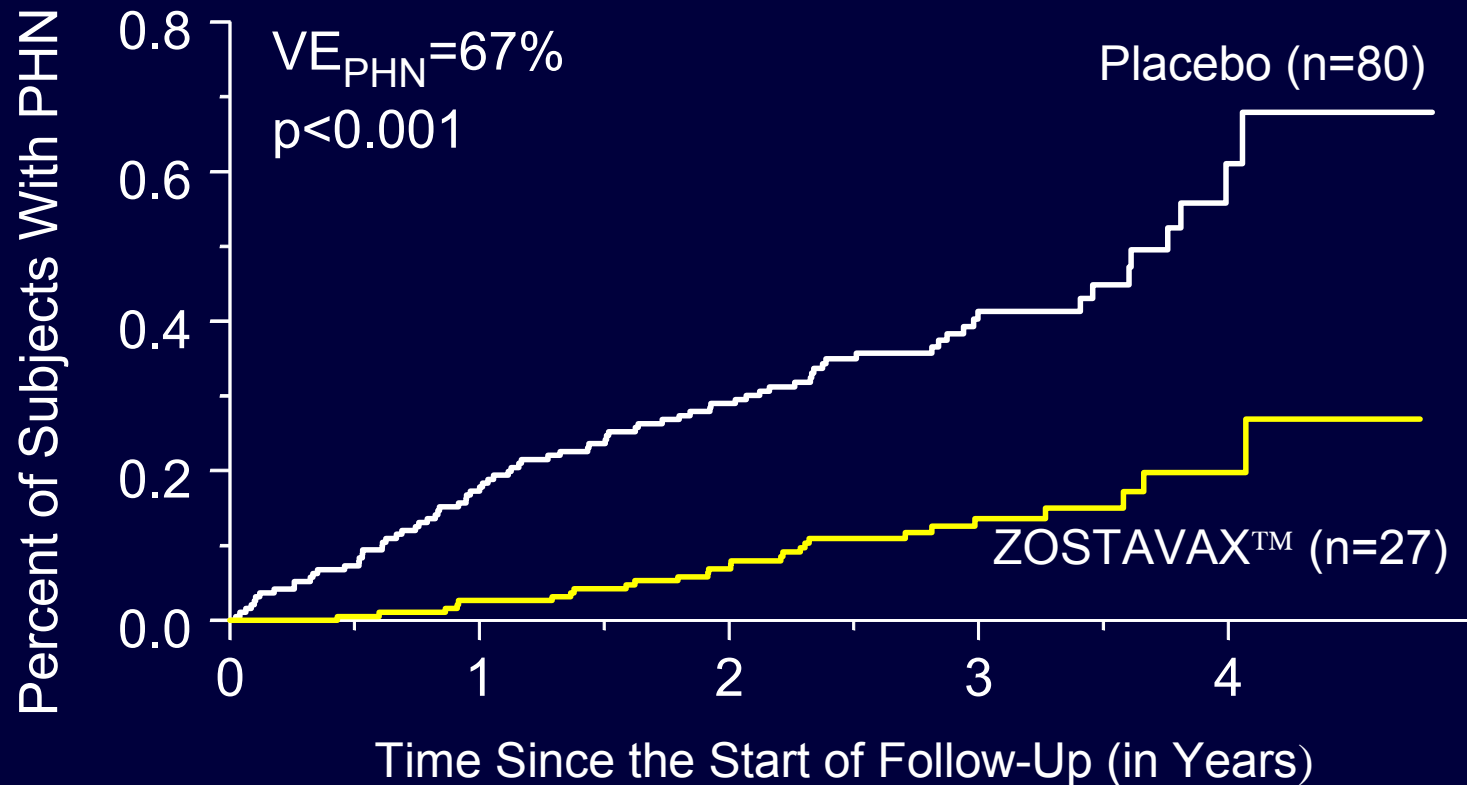
	ZOSTAVAX™ N=19,270		Placebo N=19,276		% Relative Reduction in ZOSTAVAX™ Recipients (95% CI)
	n	Incidence Rate*	n	Incidence Rate*	
Neurologic†	29	0.5	82	1.4	64.9 (45.8, 77.9)
Cutaneous	39	0.7	116	2.0	66.6 (51.7, 77.4)
Ocular involvement	14	0.2	40	0.7	65.3 (34.8, 82.6)
Sacral dermatome involvement	6	0.1	24	0.4	75.2 (37.7, 91.7)
Visceral complications	9	0.2	28	0.5	68.1 (30.5, 86.8)

* Incidence rate = per 1000 person years (total population).

† Excluding pain.

ZOSTAVAX™ Efficacy: PHN Incidence

Estimate of the Cumulative Incidence of PHN Over Time by Vaccination Group (MITT Population)



Number of subjects at risk

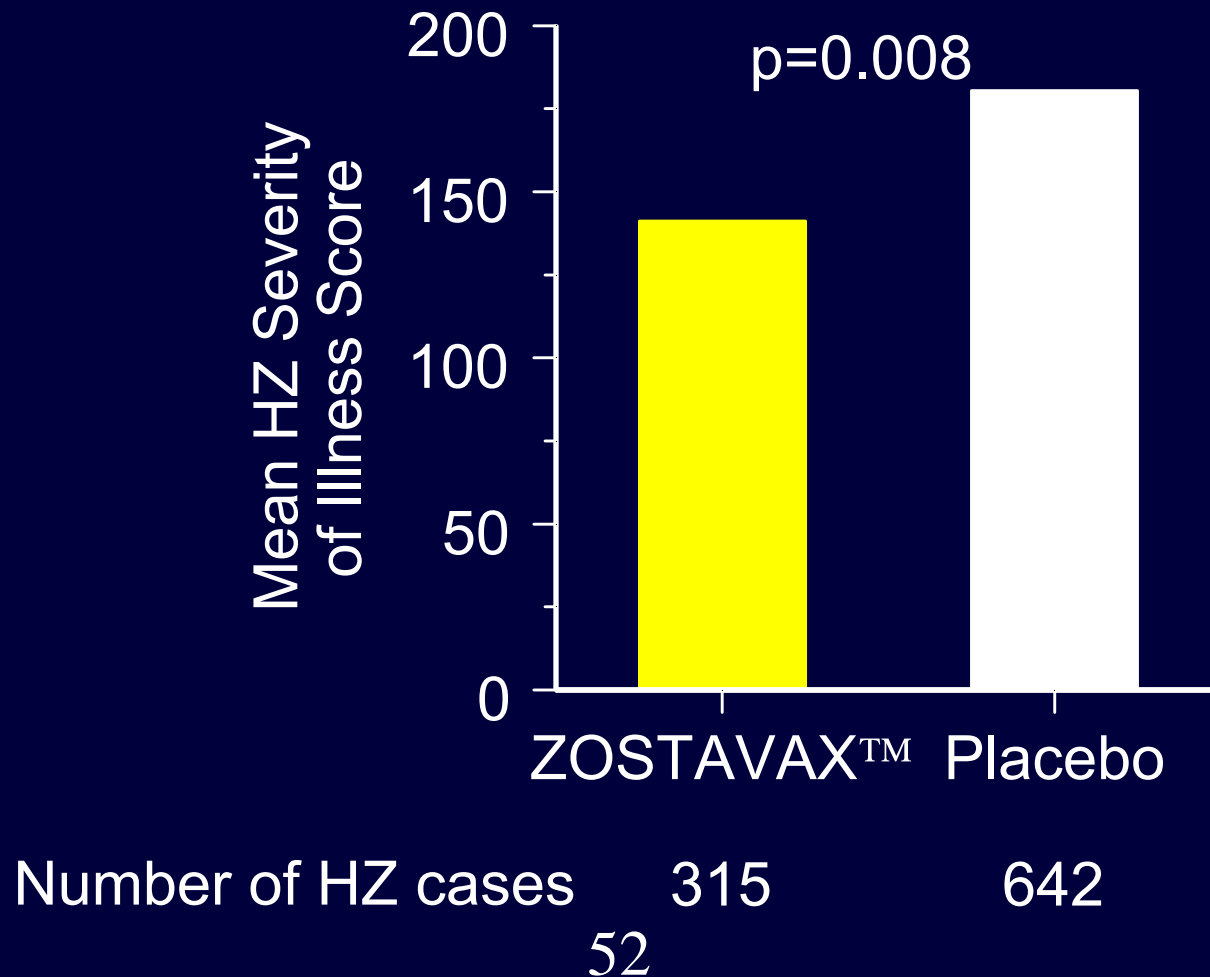
ZOSTAVAX™	19254	18994	18626	9942	1906
Placebo	19247	18915	18422	9806	1856

ZOSTAVAX™ Efficacy on HZ Pain BOI and its Components

- VE_{BOI} : 61.1% (95% CI [51.1%, 69.1%])
 - Incidence
 - Severity-by-Duration

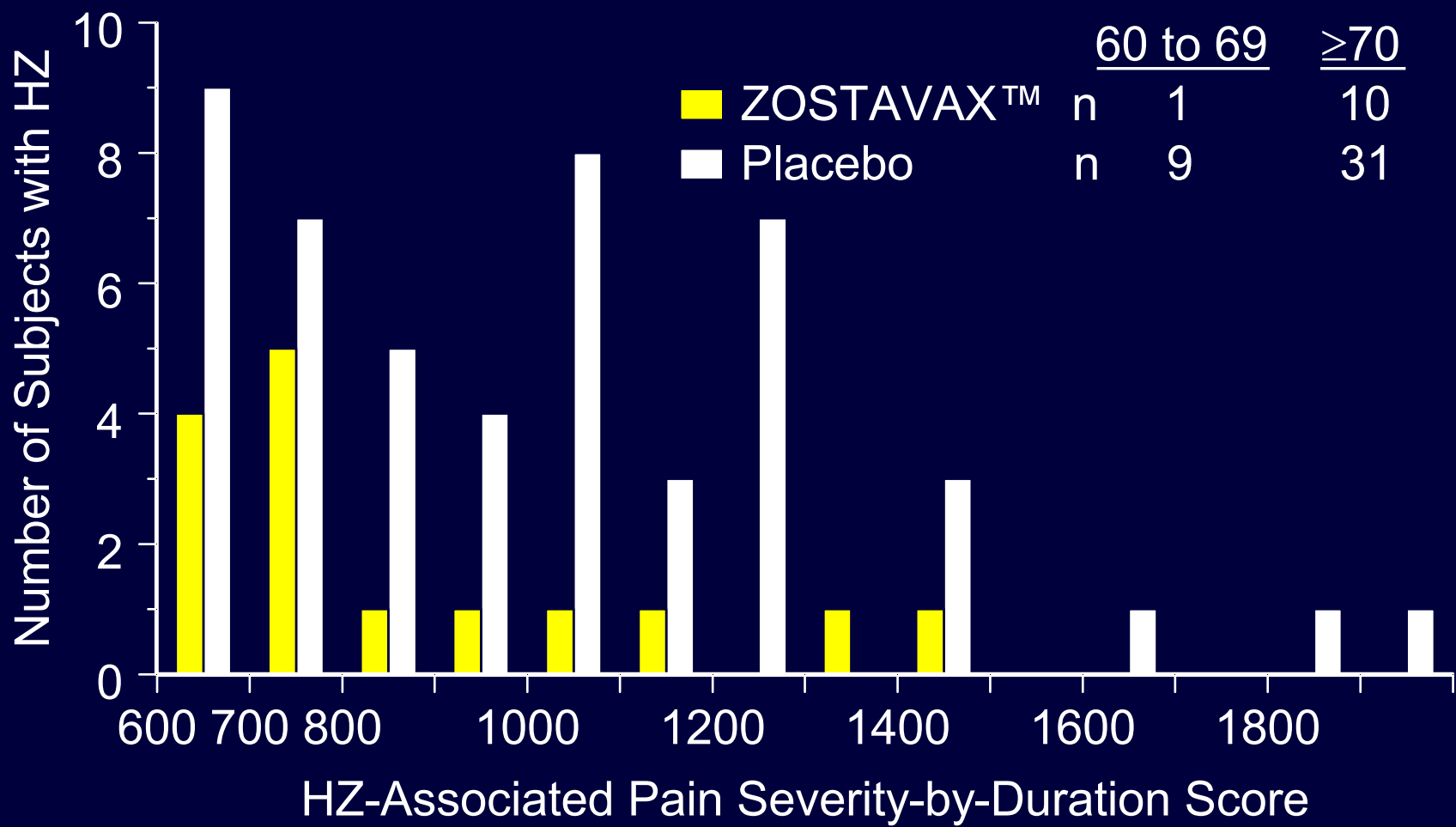
Summary of Severity-by-Duration Scores of HZ Pain Among Evaluable HZ Cases (MITT Population)

- 22% reduction in pain among vaccinated subjects



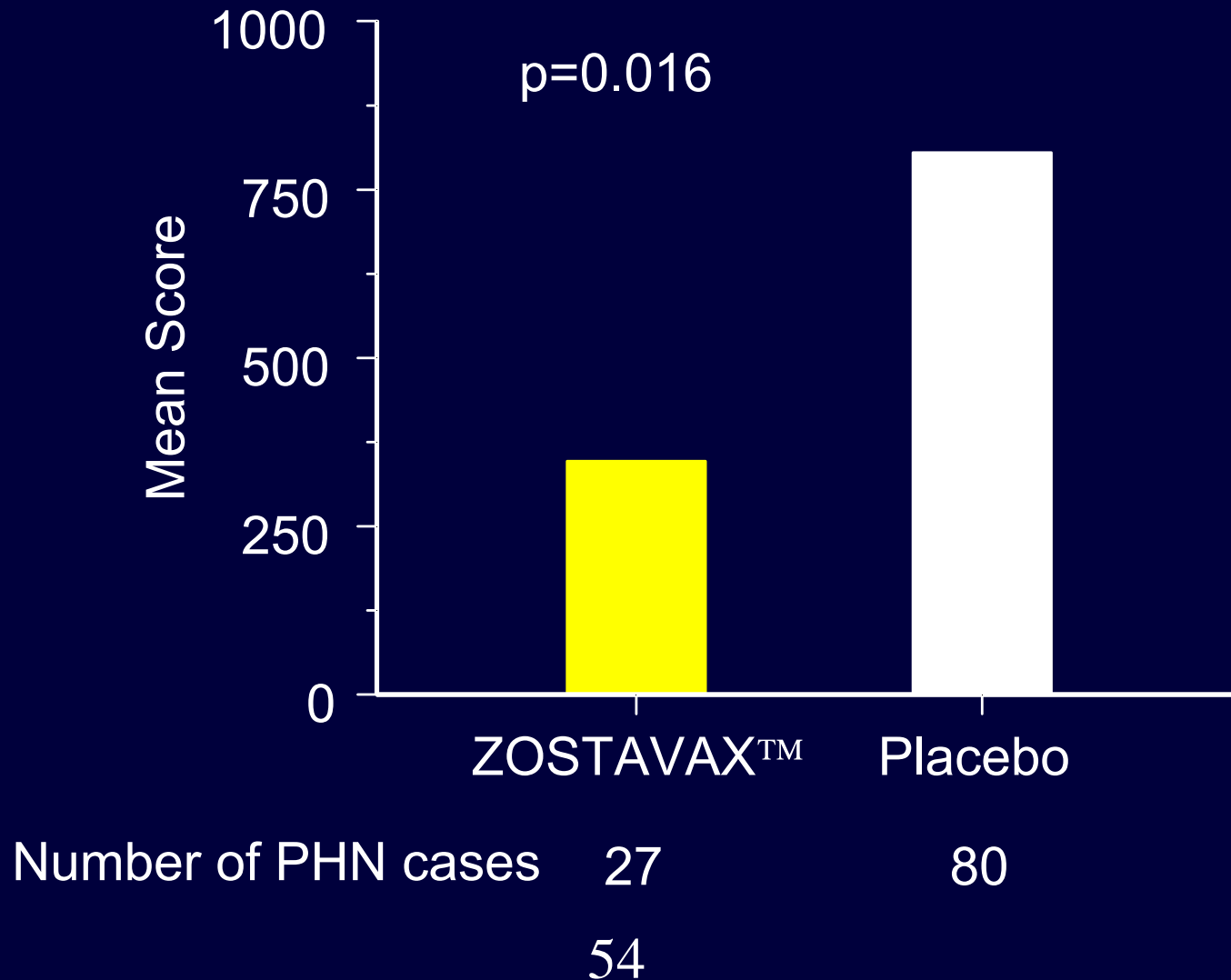
HZ Pain Severity-by-Duration (AUC) Scores Among HZ Cases with Severe, Long-Lasting HZ Pain (MITT Population)

72.6% (95% CI: 45.7%, 87.3%) reduction

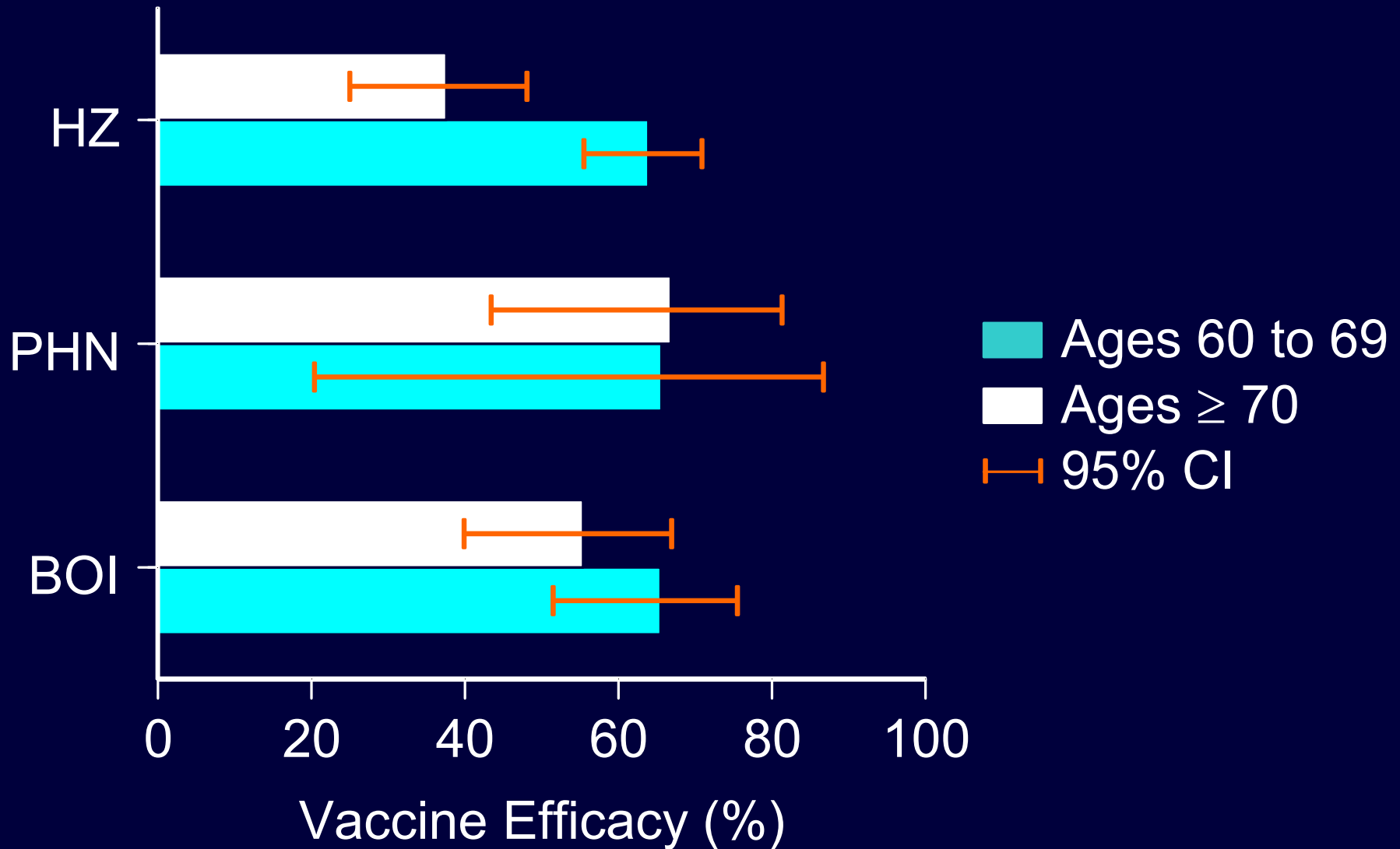


ZOSTAVAX™ Reduces the Severity-by-Duration of PHN

- 57% reduction in pain among vaccinated subjects



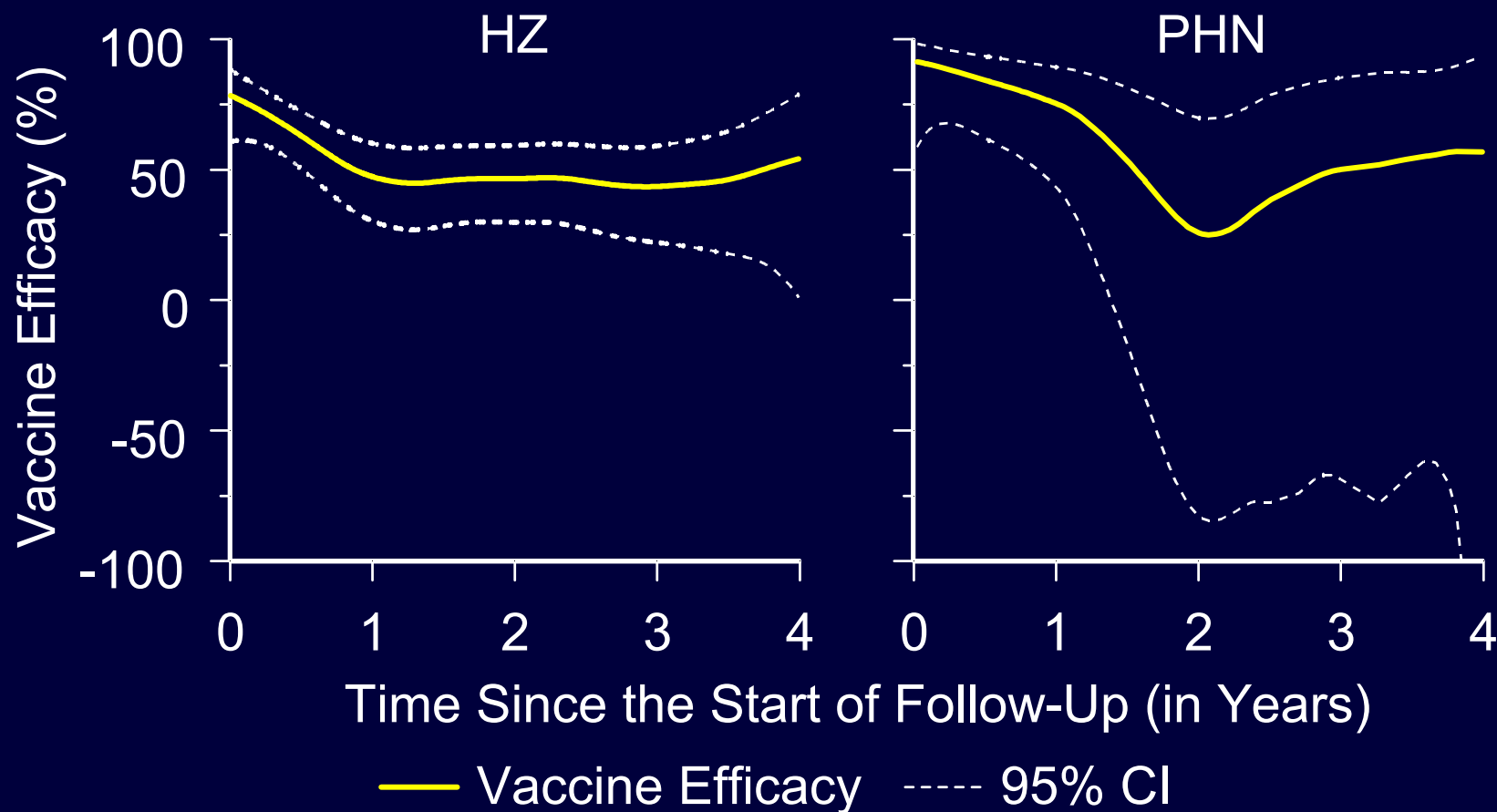
ZOSTAVAX™ Efficacy by Age Stratum



ZOSTAVAX™ Effect on Interference with Activities of Daily Living (ADL)

- Evaluated using a validated questionnaire (0-to-10 scale)
 - Average score based on 7 ADL questions
- Overall reduction in ADL interference score
 - 66.2% (95% CI: 55.4%, 74.4%)
- Reduction in incidence of moderate-to-severe ADL interference (ADL score ≥ 2 for ≥ 7 days)
 - Overall, 55.3% (95% CI: 44.2%, 64.2%)
 - Removing contribution of VE_{HZ} (prespecified endpoint), reduction was 8.2% (95% CI: -9.4%, 22.9%)

Duration of ZOSTAVAX™ Efficacy



- After initial drop during the first year, point estimates for VE_{HZ} and VE_{PHN} were stable through 48 months of follow-up
- Subject follow-up is continuing (persistence substudy) at 12 of 22 study sites

ZOSTAVAX™ Efficacy Summary

- ZOSTAVAX™ significantly reduces
 - Incidence of HZ
 - Incidence of PHN
 - BOI related to HZ pain
 - Duration of pain due to HZ
 - Risk of ADL interference due to HZ
- ZOSTAVAX™ efficacy against HZ and PHN persists through 4 years of follow-up

Discussion Topics

- Epidemiology of HZ and PHN
- Clinical Development Program
- Shingles Prevention Study
 - Study design
 - Key results
- Immunogenicity
- Safety
- Summary of Clinical Results

ZOSTAVAX™ Immunogenicity Endpoints

- Declining VZV-specific immunity is thought to be a precursor for development of HZ
- Immune responses were measured in the CMI substudy (N=1395) by:
 - VZV-specific interferon-gamma enzyme-linked immunospot (IFN- γ ELISPOT) assay
 - Glycoprotein enzyme-linked immunosorbent assay (gpELISA)
- Endpoints assessed at 6 weeks postvaccination
 - Ratio of geometric mean titer (GMT) or geometric mean count (GMC) between vaccine and placebo groups
 - Geometric mean fold rise from baseline

SPS: Immunogenicity Results

		Mean Response		
	n	Day 0	Week 6	Fold Rise (95% CI)
<hr/>				
gpELISA (units/mL)				
ZOSTAVAX™	667	278.8	474.7	1.7 (1.6, 1.8)
Placebo	684	291.0	291.4	1.0 (1.0, 1.0)
IFN-γ ELISPOT (SFC/10 ⁶ PBMC [†])				
ZOSTAVAX™	606	34.5	72.0	2.0 (1.8, 2.3)
Placebo	642	34.2	31.6	0.9 (0.8, 1.1)

[†] Spot-forming cells per 10⁶ peripheral blood mononuclear cells.

Correlation of Immune Response with Efficacy at Week 6 Postvaccination

- Regression model of correlation with efficacy:
 - gpELISA
 - IFN- γ ELISPOT
- Best correlation with clinical efficacy: gpELISA

One-log-unit Increase	HZ Risk Reduction (95% CI)	p-Value
gpELISA titers	38.0% (20.9%, 51.5%)	<0.001
ELISPOT counts	18.2% (3.6%, 30.5%)	0.017

SPS: Immune Responses by Age

- Immunogenicity by age cohort at 6 weeks postvaccination supports observed efficacy trend for HZ in SPS

	Age Group in Years	
	60 to 69 n=378	≥70 n=289
gpELISA fold rise	1.8 (1.6, 1.9)	1.6 (1.4, 1.7)
gpELISA GMT in units/mL	498.7 (453.5, 548.3)	445.2 (397.6, 498.4)

Protocol 010: Immune Responses by Age

- Immunogenicity at 4 weeks postvaccination comparable among subjects 50 to 59 years of age and older subjects

	Age Group in Years	
	50 to 59 n=45	≥60 n=68
gpELISA fold rise	2.9 (2.1, 4.0)	2.0 (1.6, 2.6)
gpELISA GMT in units/mL	646.0 (448.3, 930.9)	781.8 (583.9, 1046.8)

Immunogenicity Summary

- In the face of pre-existing immunity, ZOSTAVAX™ elicits an increase in VZV-specific immunity compared with placebo at 6 weeks postvaccination, as measured by gpELISA and IFN- γ ELISPOT
- VZV antibody response measured by gpELISA correlates well with protection against HZ

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ZOSTAVAX™ Safety Experience

- Builds on extensive VARIVAX® safety database
 - 56 million doses distributed since licensure in 1995
- Clinical evaluation in over 20,000 subjects vaccinated with ZOSTAVAX™
 - Over 19,000 placebo controls
 - Allowed for observation of uncommon adverse experiences

<u>Power</u>	<u>Ability to Detect Event with Rate</u>
97.5%	1 in 5549 (1.8 per 10,000)
80%	1 in 12,717 (0.8 per 10,000)

- ZOSTAVAX™ is well tolerated in adults ≥ 50 years of age

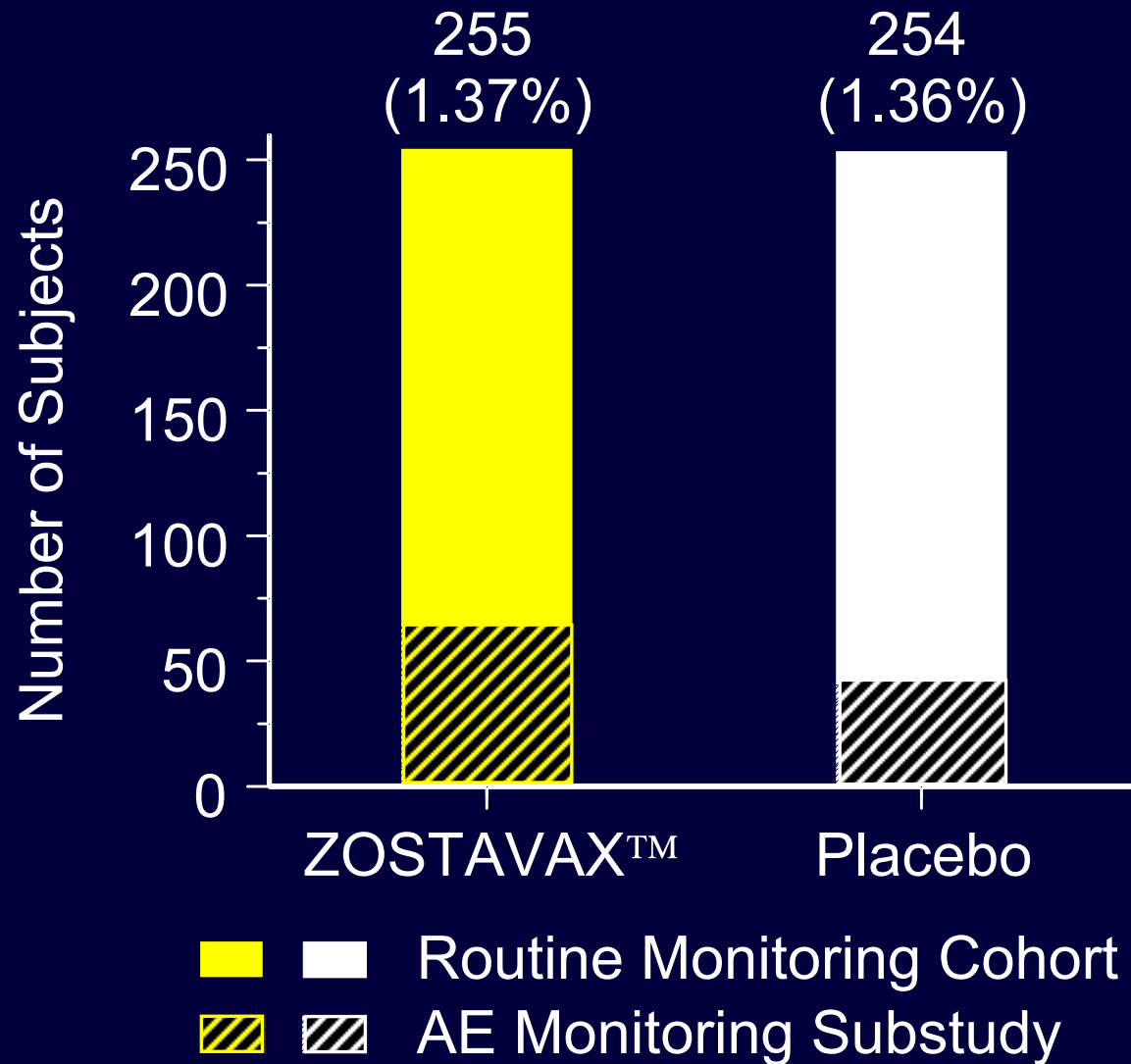
SPS: Postvaccination Safety Evaluation

- Days 0 to 42 postvaccination
 - Adverse experiences were collected on all subjects
 - Subjects were contacted shortly after Day 42 postvaccination to ascertain full reporting of serious adverse experiences
- From Day 42 postvaccination through end of study
 - Vaccine-related serious adverse experiences
 - Deaths

SPS: Adverse Event Monitoring Substudy

- Safety Substudy was conducted at all 22 study sites
 - 3345 received ZOSTAVAX™
 - 3271 received placebo
- Postvaccination safety evaluation also included:
 - Vaccination Report Card, completed through Day 42 postvaccination
 - Hospitalizations, reported until end of study

SPS: Serious Adverse Experiences



SPS: Serious Adverse Experiences

	ZOSTAVAX™ N=19,270	Placebo N=19,276
Total cohort	255 (1.37%)	254 (1.36%)
Adverse Event Substudy	64	41
Routine Monitoring Cohort	191	213
Vaccine-related SAE's	2 (0.01%)	3 [†] (0.01%)
Deaths (Day 0 to 42)	14 (0.07%)	16 (0.09%)
Deaths (entire study duration)	793 (4.1%)	792 (4.1%)
Vaccine-related discontinuation	0	0

[†] Includes 1 reported on Day 53 postvaccination.

SPS: Adverse Event Monitoring Substudy

Adverse Experience	ZOSTAVAX™ N=3345	Placebo N=3271
Local: Injection-site reaction*	48.3%	16.6%
Systemic: Overall	24.7%	23.6%
Vaccine-related*	6.3%	4.9%
Headache*	1.4%	0.9%
Elevated Temperature: ≥101.0°F (≥38.3°C)	0.8%	0.9%
Hospitalization rate (per 1000 person-years)	107.4	107.3

* Statistically significant.

Protocol 009: ZOSTAVAX™ at a Higher Potency

- Controlled, double-blind, multicenter trial
- Randomized (2:1) to receive 1 injection of ZOSTAVAX™ at a higher (207,000 PFU) or a lower potency (58,000 PFU)
- 698 subjects ≥ 50 years of age
 - Age-stratified (50 to 59 years [n=185], ≥ 60 years [n=513])
- Safety follow-up for 42 days postvaccination
- Vaccine well tolerated at both potencies administered

Safety of ZOSTAVAX™ at a Higher Potency in Subjects ≥50 Years of Age (Protocol 009)

Adverse Experiences by Age Group	Higher Potency (N=461) %	Lower Potency (N=234) %
Injection-site:		
50 to 59 years	82.9	69.4
≥60 years	55.7	56.4
Systemic:		
50 to 59 years	40.7	45.2
≥60 years	36.3	37.2
Elevated temperature ≥101.0°F (≥38.3°C):		
50 to 59 years	0.4	0.9
≥60 years	1.1	0.4

Safety Among VZV-Seronegative Subjects

- No VZV-seronegative adults detected in SPS
- VZV-seronegative adults sought in 2 protocols
 - Protocol 003 screened 1148 varicella history-negative people ≥ 30 years of age in tropical countries; n=21 enrolled
 - In Protocol 049 (adolescent/adult VARIVAX[®] study) 142 subjects were ≥ 30 years of age; n=17 were VZV-seronegative
- Conclusions regarding VZV-seronegative individuals
 - VZV-seronegativity is rare after 30 years of age
 - No safety issues identified

ZOSTAVAX™-Associated Rash

- Across the ZOSTAVAX™ database, 0.3% of subjects reported a VZV-like rash through Day 42 postvaccination
 - Oka/Merck VZV strain was identified by PCR analysis of lesion specimens from only 2 subjects
- Oka/Merck VZV strain was not identified in any SPS subject suspected of having HZ

Summary of ZOSTAVAX™ Safety Results

- ZOSTAVAX™ is well tolerated in adults ≥ 50 years of age
 - Transient injection-site reactions in about half of the vaccine recipients
- No clinically important differences between ZOSTAVAX™ and placebo with respect to
 - Serious adverse experiences
 - Systemic clinical adverse experiences
- Following a dose of ZOSTAVAX™, vaccine-associated rashes are uncommon

Discussion Topics

- Epidemiology of HZ and PHN
- Clinical Development Program
- Shingles Prevention Study
 - Study design
 - Key results
- Immunogenicity
- Safety
- Summary of Clinical Results

Rationale for Beginning Routine Zoster Vaccination at 50 Years of Age

	<u>≥50 Years of Age</u>	<u>50 to 59 Years of Age</u>	<u>≥60 Years of Age</u>
Population at risk	87MM	37MM	50MM
HZ cases preventable per year	310K to 390K	110K to 130K	200K to 260K
PHN cases preventable per year	53K to 90K	8K to 15K	45K to 75K

- Prevent work productivity loss
 - ~70% of individuals 50 to 59 years of age are employed, with an estimated 600,000 to 700,000 work days lost annually due to HZ
- Severity and healthcare use in acute HZ comparable in those 50 to 59 and 60 to 69 years of age

Rationale for Beginning Routine Zoster Vaccination at 50 Years of Age

- Efficacy
 - VE_{HZ} 64% in subjects 60 to 69 years of age
 - VE_{HZ} in the 60-to-69 age group should predict VE_{HZ} in persons 50 to 59 years of age
- Immunogenicity
 - Immune responses were comparable across age cohorts in the Shingles Prevention Study
 - Similar age-related findings were observed in other ZOSTAVAX™ clinical studies
- Safety
 - In Protocol 009, higher frequency of local reactions (mild/moderate, transient) in subjects 50 to 59 years of age than in subjects ≥ 60 years of age but generally well tolerated
 - Similar results seen in Protocol 049 among seropositive and seronegative subjects ≥ 13 years of age

Summary of ZOSTAVAX™

- Extensive ZOSTAVAX™ clinical database
 - Over 40,000 subjects enrolled; over 20,000 vaccinated
- Prevents HZ (VE=51%)
- Prevents PHN (VE=67%)
- Reduces HZ pain BOI (VE=61%)
- Efficacy persists for 4 years postvaccination
- Elicits a VZV-specific CMI response
- Has an excellent safety profile

ZOSTAVAX™ Agenda

Introduction

David Gutsch, M.D.
Director, Regulatory Affairs

Epidemiology and the Clinical Development Program

Jeffrey Silber, M.D.
Senior Director, Clinical Research

Concluding Remarks

David Gutsch, M.D.
Director, Regulatory Affairs

Ongoing/Planned ZOSTAVAX™ Activities

- Durability of efficacy in SPS subjects
- Vaccination of SPS and Protocol 007 placebo recipients
- Bridging study: Transition from frozen to refrigerated formulation
- Inactivated influenza vaccine concomitant use
- Pharmacovigilance Plan
 - Postmarketing surveillance for adverse events
 - VZV Identification Program
 - Clinical specimens submitted for PCR analysis
 - Pregnancy Registry

Benefits/Risks

- HZ and PHN are often debilitating diseases, for which there is an unmet medical need for better management
- ZOSTAVAX™ would be the first intervention to prevent HZ and its complications, including PHN
- Beyond the benefits from prevention, ZOSTAVAX™ reduces the severe pain associated with HZ and PHN
- ZOSTAVAX™ has an excellent safety profile

ZOSTAVAX™ will address important
medical and public health needs

ZOSTAVAX™ Proposed Indications

- ZOSTAVAX™ is indicated for:
 - Prevention of herpes zoster (shingles)
 - Prevention of postherpetic neuralgia (PHN)
 - Reduction of acute and chronic zoster-associated pain
- ZOSTAVAX™ is indicated for immunization of individuals 50 years of age or older