Immunogenicity and Safety of DTaP5-IPV-Hib-HepB, a Pediatric Hexavalent Combination Vaccine

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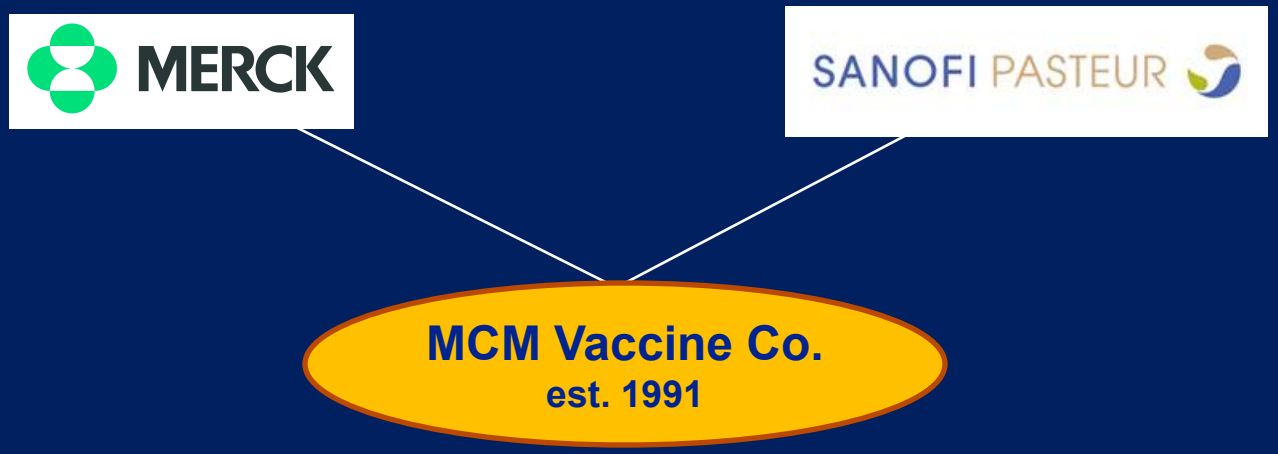
Outline

- Overview of MCM Vaccine Co., a partnership between Merck & Co., Inc., and Sanofi Pasteur Inc.
- Pediatric hexavalent vaccine composition
- Study 005 design and immunogenicity results
- Study 006 design and immunogenicity results
- Integrated safety results
- Summary

A Partnership Between Two Companies



Governance			
Manufacture	HepB, Hib	+	DTaP5, IPV Formulation, Release
Development	Clinical Lead	+	Partner
	Partner	+	Regulatory Lead
Co-Promotion	Merck	+	Sanofi Pasteur
Pharmacovigilance	Lead Holds global safety database	+	Partner

Hexavalent Vaccine Comprised of Licensed Components

Antigen(s)		Amounts in hexavalent vaccine	Licensed vaccine containing the same antigen(s)
MERCK	**PRP-OMPC** Polyribosylribitol phosphate polysaccharide coupled to the outer membrane protein complex of *Neisseria meningitidis*	3 µg	PEDVAX HIB®
	HBsAg Recombinant hepatitis B surface antigen	10 µg	RECOMBIVAX HB®
SANOFI PASTEUR	**5 component acellular pertussis** • PT: Pertussis Toxoid • FHA: Filamentous Hemagglutinin • PRN: Pertactin • FIM: Fimbriae Types 2 and 3 **Diphtheria Toxoid** **Tetanus Toxoid**	 20 µg 20 µg 3 µg 5 µg 15 Lf (≥20 IU) 5 Lf (≥40 IU)	DAPTACEL®
	IPV - Inactivated Poliovirus • Type 1 • Type 2 • Type 3	 29-DU 7-DU 26-DU	IPOL®

PENTACEL®

Aluminium (0.319 mg) used as adjuvant

Fully liquid formulation requires no reconstitution, simplifying administration

Hib Antigen Amount in Final Hexavalent Vaccine (HV) Formulation Based on Phase II Results

	Postdose 3 Observed PRP Responses (95% CI)			
	HV PRP-T 12 µg n = 170	HV PRP-OMPC 3 µg n = 167	HV PRP-OMPC 6 µg n = 158	Pentacel® + Recombivax HB® n = 154
% ≥1.0 µg/mL	68.2% (60.7%, 75.2%)	95.8% (91.6%, 98.3%)	95.6% (91.1%, 98.2%)	80.5% (73.4%, 86.5%)
Geometric Mean Antibody Conc (µg/mL)	1.9 (1.5, 2.5)	9.9 (8.1, 12.2)	11.9 (9.7, 14.6)	3.9 (3.1, 5.0)

PRP-T = polyribosylribitol phosphate–tetanus toxoid conjugate; PRP-OMPC = PRP-*Neisseria meningitidis* outer membrane protein complex conjugate; n = number of participants with results

- PRP-OMPC-containing formulations of the HV had acceptable Hib responses; whereas, PRP-T formulation did not
- HV PRP-OMPC 3 µg and 6 µg formulations had similarly high Hib responses
  - 6 µg formulation associated with slightly higher rates of injection-site and systemic adverse events
- HV PRP-OMPC 3 µg was chosen for further development

Diaz-Mitoma et al. Vaccine 29 (2011) 1324–1331.

Comparison of US Combination Vaccine Schedules

Vaccines	2 months	4 months	6 months	15-18 months	Total Shots
DTaP-HepB-IPV*	X	X	X	DTaP†	7 or 8
Hib	X	X	(X)	X	
DTaP-IPV/Hib‡	X	X	X	X	6
HepB	X		X		
Hexavalent Vaccine (HV)	X	X	X		4 or 5
DTaP-IPV/Hib‡				X	
DTaP§ + Hib				X + X	

* Pediarix® (GlaxoSmithKline)
† Infanrix® (GlaxoSmithKline)
‡ Pentacel® (Sanofi Pasteur)
§ Daptacel® (Sanofi Pasteur)
X denotes an injection

- HV regimen has 2 to 4 less injections than Pediarix® + Hib, depending on monovalent Hib
- HV regimen has 1 to 2 less injections than Pentacel® + HepB, depending on toddler vaccine(s)

Study 005 Design

Group	Infant Series				Toddler Dose	Close-out
	2 months	4 months	6 months	7 months	15 months	16 months
1 (N=960)	*Blood Draw* Hexavalent Vaccine (HV) Prevnar 13 RotaTeq	HV Prevnar 13 RotaTeq	HV Prevnar 13 RotaTeq	*Blood Draw*	*Blood Draw* Daptacel PedvaxHIB Prevnar 13	*Blood Draw*
2 (N=480)	*Blood Draw* Pentacel Recombivax HB Prevnar 13 RotaTeq	Pentacel Prevnar 13 RotaTeq	Pentacel Recombivax HB Prevnar 13 RotaTeq		*Blood Draw* Daptacel ActHIB Prevnar 13	

- Pivotal US non-inferiority to licensed component control study (Postdose 3 and Postdose 4)
- Immunogenicity of RotaTeq (Postdose 3)

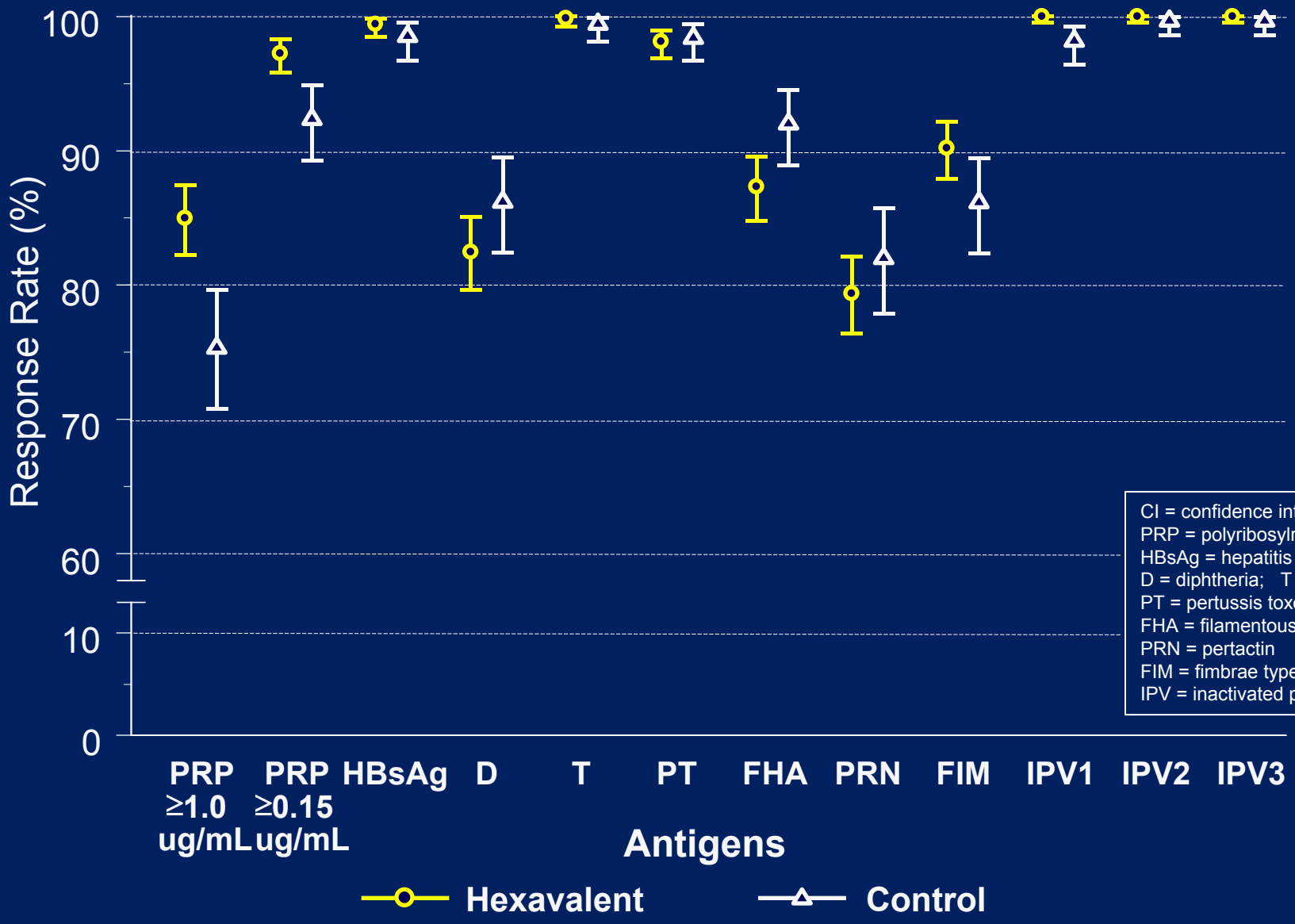
Prevnar13®: Pneumococcal 13-valent Conjugate Vaccine (Pfizer); **RotaTeq®**: Rotavirus Vaccine, Live, Oral, Pentavalent (Merck)
Daptacel®: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur); **Pedvax HIB®**: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (Merck); **Pentacel®**: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur); **Recombivax HB®**: Hepatitis B Vaccine (Recombinant) (Merck); **ActHIB®**: Haemophilus B conjugate vaccine (tetanus toxoid conjugate) (Sanofi Pasteur)

Marshall et al. Pediatrics 136 (2015) e323-332.

Study 005: Immunogenicity Endpoints

- Primary
  - Non-inferiority of antibody response rates to all hexavalent vaccine (HV) antigens at one month Postdose 3 in HV vs control vaccine recipients
  - Non-inferiority of pertussis antibody geometric mean concentrations (GMCs) at one month Postdose 3 and at one month Post-Toddler dose in recipients of HV vs control vaccine infant doses
  - Acceptably high polio antibody titers at one month Postdose 3 in HV recipients
- Secondary
  - Non-inferiority of proportion of HV vs control vaccine recipients with anti-polyribosylribitol phosphate (PRP) concentrations ≥0.15 µg/mL at one month Postdose 3
  - Non-inferiority of PRP GMCs at one month Postdose 3 in HV vs control vaccine recipients
  - Non-inferiority of anti-rotavirus IgA GMCs at one month Postdose 3 in HV vs control vaccine recipients

Study 005: Antibody Response Rates and 95% CIs at One Month Postdose 3



CI = confidence interval
PRP = polyribosylribitol phosphate
HBsAg = hepatitis B surface antigen
D = diphtheria; T = tetanus
PT = pertussis toxoid
FHA = filamentous haemagglutinin
PRN = pertactin
FIM = fimbrae types 2 and 3
IPV = inactivated poliovirus

Study 005: Non-Inferiority Analysis of Pertussis Antibody Responses and Concentrations at One Month Postdose 3

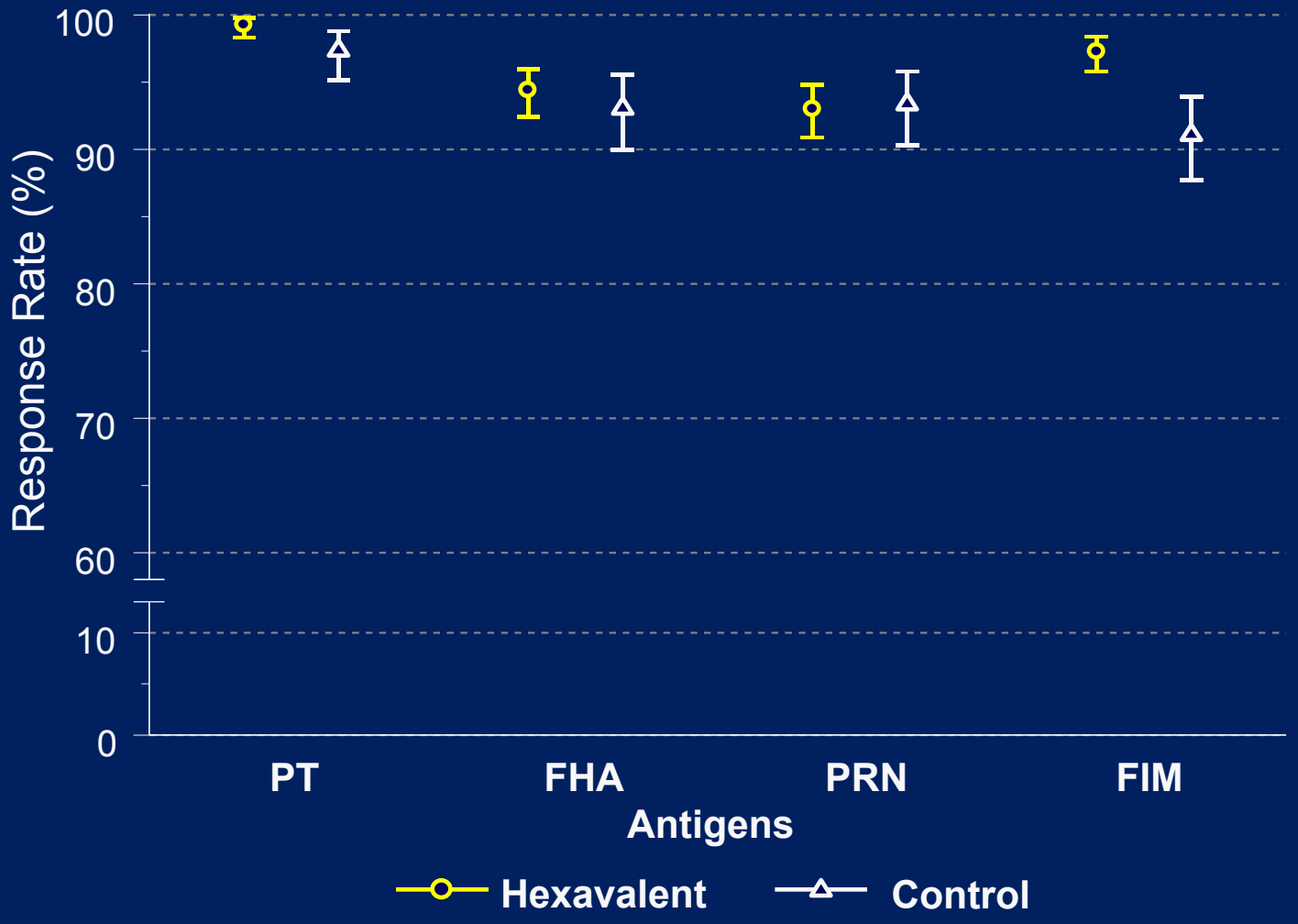
Antigen	Endpoint	Hexavalent (N = 924)		Control (N = 460)		Estimated Response Difference / GMC Ratio (95% CI)	NI Margin	Conclusion: Non-Inferiority Criterion Met / Not Met
		n	Estimated Response / GMC	n	Estimated Response / GMC			
PT	% vaccine response	796	98.1	391	98.5	-0.33 (-1.80, 1.60)	-10%	Met
	GMC	810	109.6	400	85.4	1.28 (1.20, 1.38)	0.67	Met
FHA	% vaccine response	796	87.3	391	92.0	-4.70 (-8.14, -0.97)	-10%	Met
	GMC	810	46.6	400	72.3	0.64 (0.59, 0.70)	0.67	Not Met
PRN	% vaccine response	794	79.3	390	82.0	-2.67 (-7.27, 2.23)	-10%	Met
	GMC	808	55.8	400	66.8	0.83 (0.73, 0.95)	0.67	Met
FIM	% vaccine response	796	90.2	391	86.2	4.05 (0.23, 8.28)	-10%	Met
	GMC	809	235.9	400	184.4	1.28 (1.15, 1.42)	0.67	Met

N = participants in analysis population; n = number of participants with results GMC = geometric mean concentration; CI = confidence interval; NI = non-inferiority

The pertussis vaccine response was defined as follows: (1) if prevaccination antibody concentration was < 4X the lower limit of quantitation (LLOQ), then the postvaccination antibody concentration was ≥ 4X LLOQ; (2) if prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination level. The prevaccination level was defined as the antibody concentration before Dose 1.

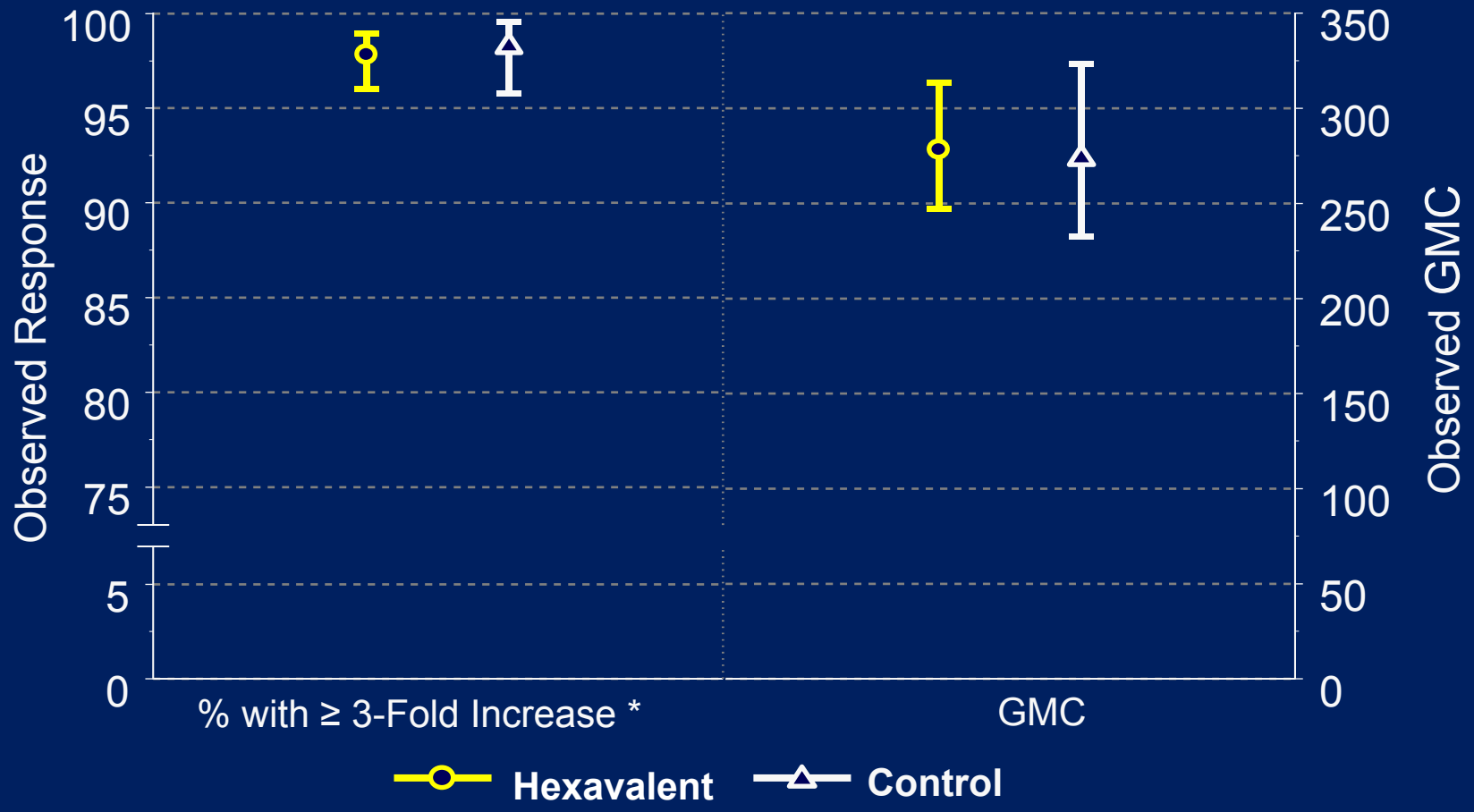
- Postdose 3 non-inferiority criteria met for all pertussis antibody endpoints except FHA GMC

Study 005: Pertussis Antigen Response Rates (with 95% CIs) at One Month Post-Toddler Dose



- Post-toddler dose non-inferiority criteria met for all pertussis antibody endpoints

Study 005: Summary of Serum Anti-Rotavirus IgA Responses (with 95% CI) at One Month Postdose 3



- Rotavirus immunogenicity non-inferior when given with hexavalent vs control vaccines

* Increase from Baseline to Postdose 3
CI = confidence interval; GMC = geometric mean concentration

Study 006 Design

Group	Infant Series				Toddler Dose	Close-out
	2 months	4 months	6 months	7 months	15 months	16 months
1 (N=800)	*Blood Draw* Hexavalent Vaccine (HV) , Lot A Prevnar 13 RotaTeq	HV, Lot A Prevnar 13 RotaTeq	HV, Lot A Prevnar 13 RotaTeq	*Blood Draw*	*Blood Draw* Pentacel Prevnar 13	*Blood Draw*
2 (N=800)	*Blood Draw* HV, Lot B Prevnar 13 RotaTeq	HV, Lot B Prevnar 13 RotaTeq	HV, Lot B Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	
3 (N=800)	*Blood Draw* HV, Lot C Prevnar 13 RotaTeq	HV, Lot C Prevnar 13 RotaTeq	HV, Lot C Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	
4 (N=400)	*Blood Draw* Pentacel Recombivax HB Prevnar 13 RotaTeq	Pentacel Prevnar 13 RotaTeq	Pentacel Recombivax HB Prevnar 13 RotaTeq		*Blood Draw* Pentacel Prevnar 13	

- Lot Consistency Study (Postdose 3)
  - Consistent immune responses to all antigens were shown across 3 lots
- Immunogenicity of Prevnar 13 (Postdose 3)

Study 006: Non-Inferiority Analysis of Pertussis Antibody Responses at One Month Post-Toddler Dose

Antigen	Endpoint	Hexavalent (N = 2002)		Control (N = 326)		Estimated Difference / GMC Ratio (95% CI)	NI Margin
		n	Estimated Response / GMC	n	Estimated Response / GMC		
PT	% vaccine response	1616	98.5	254	98.4	0.12 (-1.11, 2.58)	-10%
	GMC	1744	104.9	271	98.3	1.07 (0.98, 1.17)	0.67
FHA	% vaccine response	1669	95.3	261	95.5	-0.16 (-2.41, 3.22)	-10%
	GMC	1742	99.0	271	114.7	0.86 (0.79, 0.95)	0.67
PRN	% vaccine response	1608	92.2	258	91.0	1.15 (-2.13, 5.47)	-10%
	GMC	1746	105.3	271	141.9	0.74 (0.66, 0.83)	0.67
FIM	% vaccine response	1664	93.0	264	90.0	3.00 (-0.39, 7.40)	-10%
	GMC	1746	426.4	271	325.9	1.31 (1.17, 1.46)	0.67

N = participants in analysis population; n = number of participants with results; GMC = geometric mean concentration; CI = confidence interval; NI = non-inferiority

The pertussis vaccine response was defined as follows: (1) if prevaccination antibody concentration was < 4X the lower limit of quantitation (LLOQ), then the postvaccination antibody concentration was ≥ 4X LLOQ; (2) if prevaccination antibody concentration was ≥ 4X LLOQ, then the postvaccination antibody concentration was ≥ prevaccination level. The prevaccination level was defined as the antibody concentration before Dose 1.

Study 006: Analysis of Anti-Pneumococcal (PN) Responses One Month Postdose 3

Antigen	Hexavalent (N = 2232)		Control (N = 370)		GMC Ratio (95% CI)	NI Margin	NI Criterion Met / Not Met
	n	Estimated GMC	n	Estimated GMC			
PN 1	1256	1.38	191	1.50	0.92 (0.82, 1.04)	0.67	Met
PN 3	1255	0.48	191	0.51	0.95 (0.84, 1.06)	0.67	Met
PN 4	1255	1.19	189	1.19	1.00 (0.89, 1.12)	0.67	Met
PN 5	1256	1.42	191	1.53	0.93 (0.80, 1.07)	0.67	Met
PN 6A	1251	2.52	191	2.89	0.87 (0.77, 0.99)	0.67	Met
PN 6B	1255	0.96	190	1.22	0.79 (0.64, 0.96)	0.67	Not Met
PN 7F	1256	2.68	191	3.02	0.89 (0.80, 0.99)	0.67	Met
PN 9V	1256	1.31	189	1.31	1.00 (0.88, 1.13)	0.67	Met
PN 14	1256	4.66	191	4.90	0.95 (0.82, 1.10)	0.67	Met
PN 18C	1253	1.57	191	1.78	0.89 (0.79, 1.00)	0.67	Met
PN 19A	1254	1.56	191	1.71	0.91 (0.80, 1.03)	0.67	Met
PN 19F	1256	2.14	191	2.21	0.97 (0.87, 1.08)	0.67	Met
PN 23F	1254	1.05	190	1.16	0.90 (0.77, 1.06)	0.67	Met

PN 6B response missed NI study endpoint but would have satisfied Prevnar 13 NI criterion (>0.5)

N = participants in analysis population; n = number of participants with results GMC = geometric mean concentration; NI = Non-inferiority

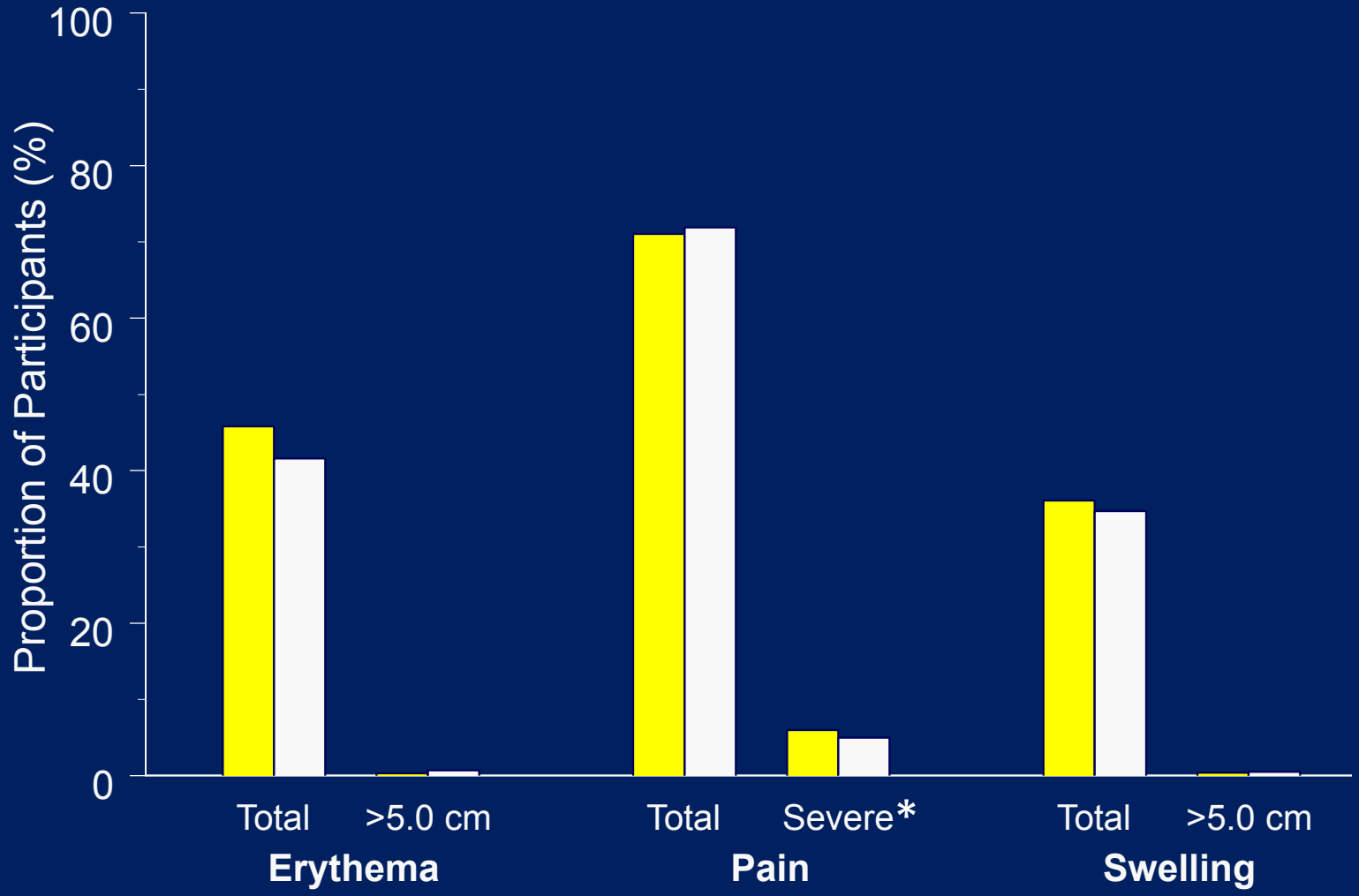
Safety Measurements for US Studies

- Daily temperature measurements for 5 days after each vaccination
  - Day of vaccination counted as Day 1

38.0 ≤ Mild ≤ 38.4°C	100.4 ≤ Mild ≤ 101.1°F
38.5 ≤ Moderate ≤ 39.4°C	101.3 ≤ Moderate ≤ 102.9°F
Severe ≥ 39.5°C	Severe ≥ 103.1°F

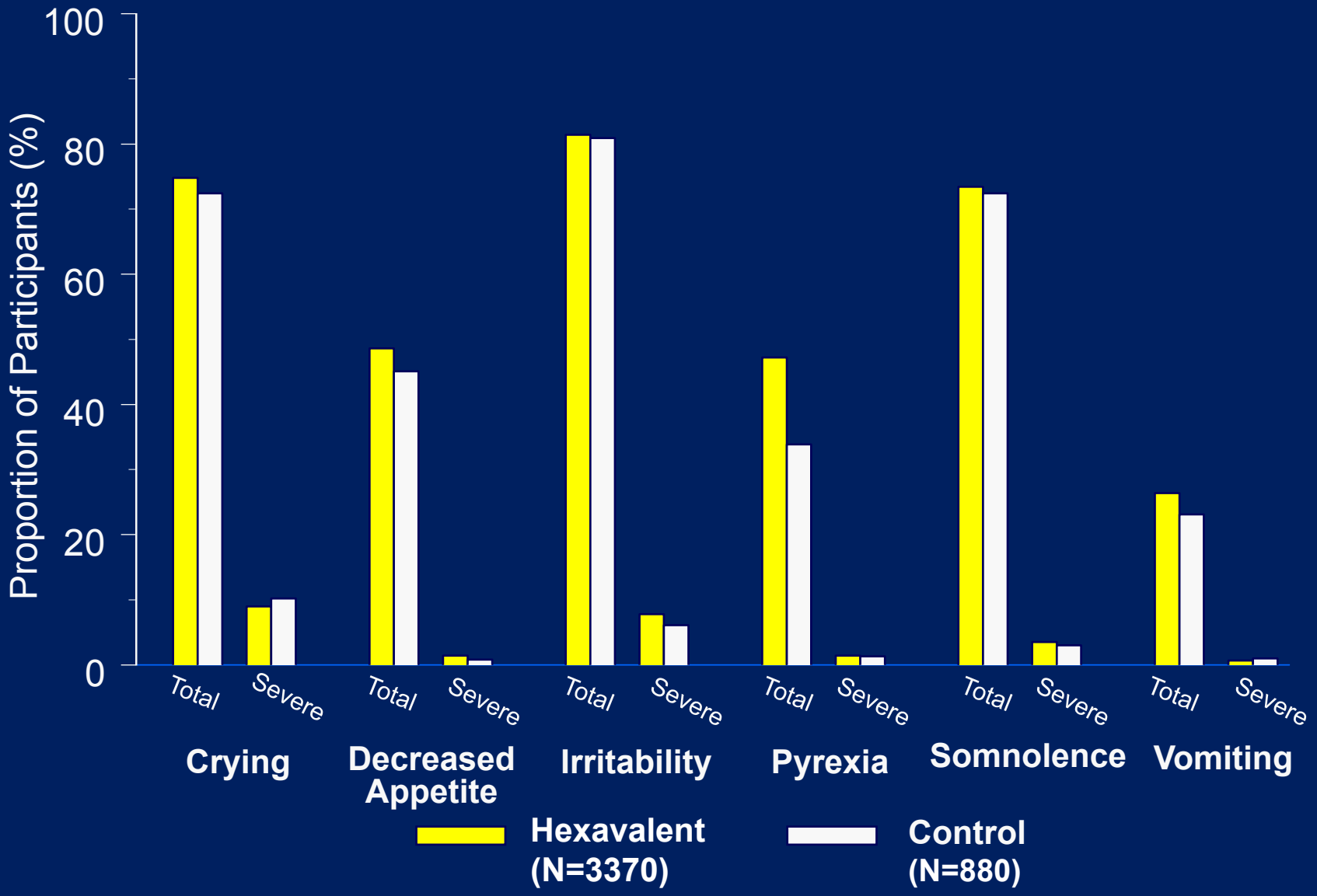
- Solicited adverse events (AEs) for 5 days after each vaccination
  - Solicited systemic AEs: fever, vomiting, crying abnormal, drowsiness, appetite loss, irritability
  - Solicited injection-site AEs: redness, swelling, and pain/tenderness
- Unsolicited AEs for 15 days after each vaccination
- Serious adverse events for ~180 days (~6 months) after infant vaccination series and for 15 days after the toddler vaccinations
- Deaths and vaccine-related serious adverse events at any time during the study

Studies 005 and 006 Combined: Percent of Participants With Any Solicited Injection-Site Adverse Events Day 1 Thru Day 5 Following Any Infant Vaccination



* Severe pain is defined as infant cries when injected limb is moved or the movement of the injected limb is reduced.

Studies 005 and 006 Combined: Percent of Participants With Any Solicited Systemic Adverse Events Day 1 Thru Day 5 Following Any Infant Vaccination



Studies 005 and 006 Combined: Summary of Participants With Fever by Severity Day 1 Thru Day 5 Following Any Infant Vaccination

	Hexavalent N = 3370		Control N = 880		Difference*	
	n	(%)	n	(%)	Estimate	(95% CI)
Participants with temperature data	3257	(96.6)	848	(96.4)	4105	(96.6)
Participants with no temperature data	113	(3.4)	32	(3.6)	145	(3.4)
Maximum Temperature (All Routes†)						
< 38.0°C	1658	(50.9)	546	(64.4)	-13.5	(-17.4, -9.6)
≥ 38.0°C and < 38.5 °C (Mild)	858	(26.2)	178	(21.9)	4.3	(0.8, 7.6)
≥ 38.5°C and < 39.5 °C (Moderate)	666	(20.6)	114	(12.5)	8.2	(5.2, 10.8)
≥ 39.5°C (Severe)	75	(2.3)	10	(1.2)	1.1	(-0.1, 1.9)

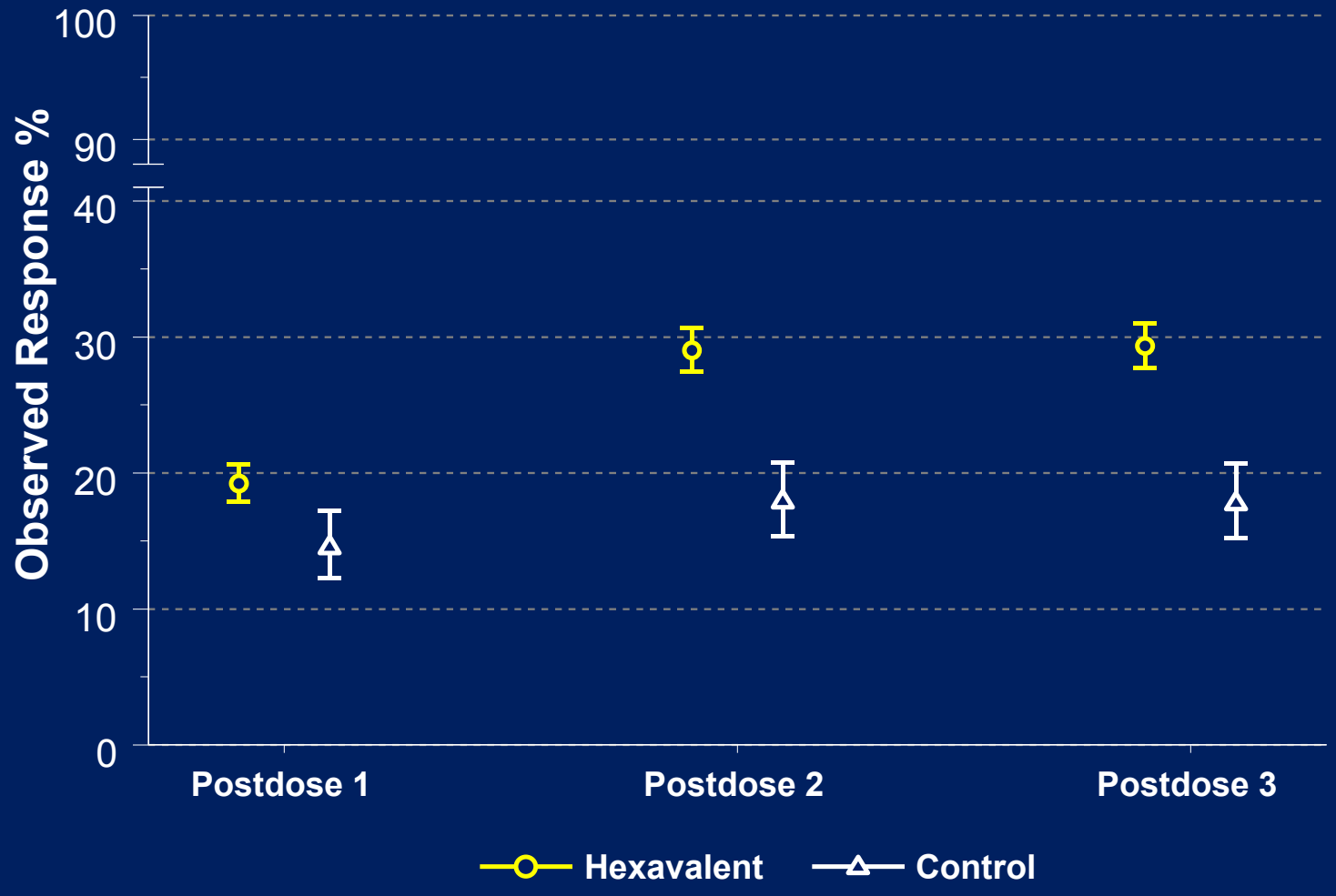
* Difference was Hexavalent group minus Control group. Estimated rate and difference were based on Miettinen and Nurminen method stratified by studies.

† Temperatures were those actually recorded, with no adjustments to the measurement route; > 90% of temperature measurements were by the rectal route.

N = number of participants in arms of combined studies; n = number of participants with results; CI = confidence interval

- Statistically significant differences in overall, mild, and moderate temperature elevations
- No significant difference observed in severe temperature elevations
- Vast majority of temperature elevations were 2 days or less in duration

Studies 005 and 006 Combined: Summary of Participants With Fever ≥ 38°C by Dose Day 1 Thru Day 5 Following Each Infant Vaccination



Studies 005 and 006 Combined: Pyrexia, Febrile Convulsion, Convulsion Following Any Infant Vaccination

	Hexavalent N = 3370 n (%)	Control N = 880 n (%)
Adverse Events (Days 1 thru 15)		
Pyrexia	1627 (48.3)	310 (35.2)
Febrile convulsion	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)
Serious Adverse Events (SAE) (Days 1 thru 15)		
Pyrexia	3 (0.1)	0 (0.0)
Febrile convulsion	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)
Serious Adverse Events (Days 1 thru 181*)		
Pyrexia	4 (0.1)	1 (0.1)
Febrile convulsion†	5 (0.1)	0 (0.0)
Convulsion†	1 (0.0)	2 (0.2)

* Covers period from 1st infant vaccination through day 181 after 3rd vaccination.

† SAEs of febrile convulsion and convulsion occurred outside of the 15-day safety follow-up period and were considered by the investigator to be unrelated to the study vaccines.

N = number of participants in arms of combined studies; n = number of participants with results

- Low and similar incidence of pyrexia SAEs for hexavalent and control vaccines
- No febrile seizures within 15 days of vaccination

Studies 005 and 006 Combined: Summary of Participants With Serious Vaccine-Related Adverse Events and Participants Who Discontinued Due to an Adverse Event

	Hexavalent N = 3370		Control N = 880		Difference*	
	n	(%)	n	(%)	Estimate	(95 % CI)
Number and percentage of participants:						
With serious vaccine-related adverse events	6	(0.2)	0	(0.0)	0.2	(-0.4, 0.4)
Who died	6	(0.2)	1	(0.1)	0.1	(-0.5, 0.3)
Discontinued due to an adverse event	8	(0.2)	1	(0.1)	0.2	(-0.4, 0.4)
Discontinued due to a vaccine-related adverse event	2	(0.1)	1	(0.1)	-0.0	(-0.6, 0.2)
Discontinued due to a serious adverse event	3	(0.1)	0	(0.0)	0.1	(-0.4, 0.3)
Discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0	(-0.5, 0.1)

* Difference was Hexavalent group minus Control group

N = number of participants in arms of combined studies; n = number of participants with results; CI = confidence interval

- Low incidence of vaccine-related serious adverse events and study discontinuations due to adverse events in both vaccination groups
- None of the deaths were considered vaccine-related

Overall Summary of the Pediatric Hexavalent Vaccine (HV) in the US

- Investigational product under review by the FDA
- Demonstrated robust immunogenicity and acceptable safety profile in rigorous Phase III studies with a total of over 4,250 infants
  - Infant series immune responses were non-inferior to control, except for GMC of FHA (however, FHA response rates were non-inferior)
  - Increase in self-limited, mild-to-moderate fever was observed, but was not associated with increases in clinical consequences
  - Concomitant rotavirus and pneumococcal conjugate vaccine immunogenicity was similar when given with HV or control
- Combination vaccines improve vaccination compliance and timeliness
- This DTaP5-IPV-Hib-HepB vaccine will provide a new option for meeting the recommended US vaccination schedule with fewer injections