



# V114 Ph-3 Pediatric Clinical Development Program

*Update for the ACIP*

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# Presentation topics

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## **Additional V114 safety data in the Ph-3 Pediatric Program**

- Pediatric safety database (7 studies in US filing)
- PD4 solicited daily temperatures  $\geq 104^{\circ}\text{F}$  and clinical outcomes (integrated analysis)

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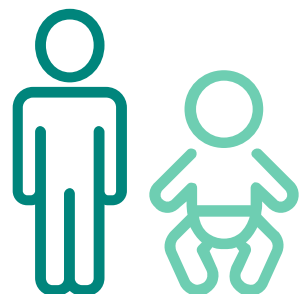
## **Summary of key additional analyses submitted in support of the V114 Pediatric US filing**

- Executive Summary
- Conclusions



# Additional V114 Safety Data in the Ph-3 Pediatric Program

## V114 Pediatric safety database - US filing (7 studies)



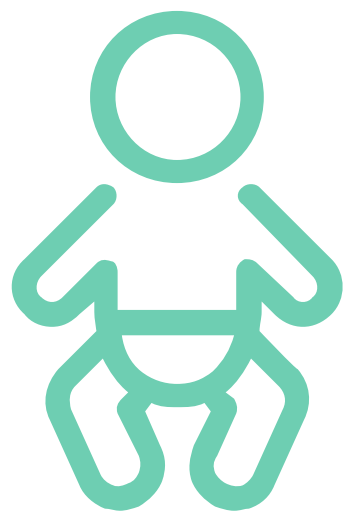
**7**  
**Clinical**  
**trials**



~7,200 participants (6 weeks to 17 years of age)

of whom

~4,800 received V114



**Healthy**  
**Infants**



~6,100 participants (6 to 12 weeks of age)

of whom

~4,300 received V114

**Integrated**  
**infant (ISS)**  
**population**  
(3 studies\*)



~4,500 participants (6 to 12 weeks of age)

of whom

~3,000 received V114

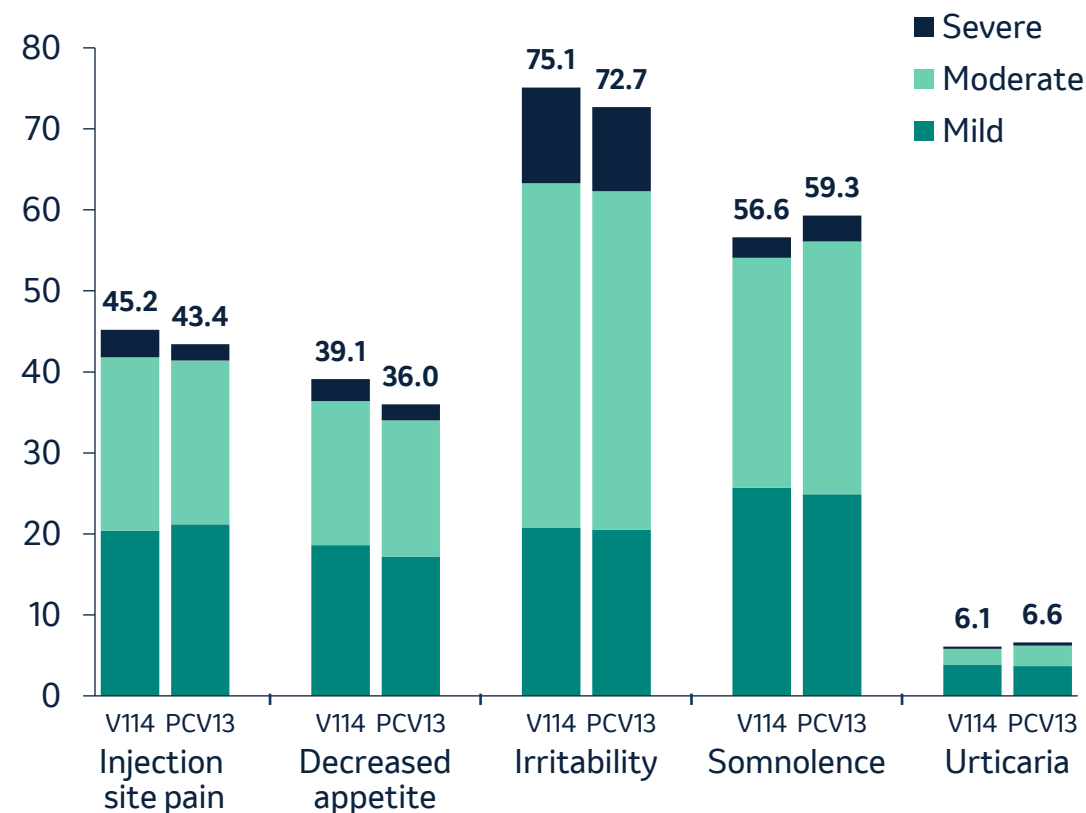
\*Safety data following administration of PCV were pooled across 3 Phase 3 studies (ISS: P027, P029, P031) based on similarities in study population and study design; for V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included in the ISS.

# ISS: The safety profile of V114 is generally comparable to PCV13

Summary of AEs following any dose	V114 N=3002	PCV13 N=1467
	n (%)	n (%)
≥1 AE	2,808 (93.5)	1,362 (92.8)
Injection-site AEs	2,074 (69.1)	989 (67.4)
Systemic AEs	2,730 (90.9)	1,320 (90.0)
<b>Vaccine-related AEs</b>	2,674 (89.1)	1,268 (86.4)
Injection-site AEs	2,071 (69.0)	987 (67.3)
Systemic AEs	2,411 (80.3)	1,106 (75.4)
<b>Serious AEs</b>	301 (10.0)	147 (10.0)
Serious vaccine-related AEs	2 (0.1)	0 (0.0)
<b>Who died</b>	2 (0.1)	2 (0.1)
Who discontinued vaccine due to an AE	0 (0.0)	0 (0.0)

AE = adverse event. Vaccine-related AEs were those determined by the investigator to be related to the vaccine. Reported adverse events include nonserious adverse events that occurred within 14 days of any vaccination and serious adverse events that occurred after dose 1 through completion of study participation.

## % of Participants




Injection site pain, decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following each dose. For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.

# How is temperature assessed in V114 pediatric clinical trials?



1  
Upon enrollment, parents are given a digital thermometer and electronic vaccination report card (eVRC)

2  
 Parents are prompted by the eVRC to enter daily maximum body temperatures

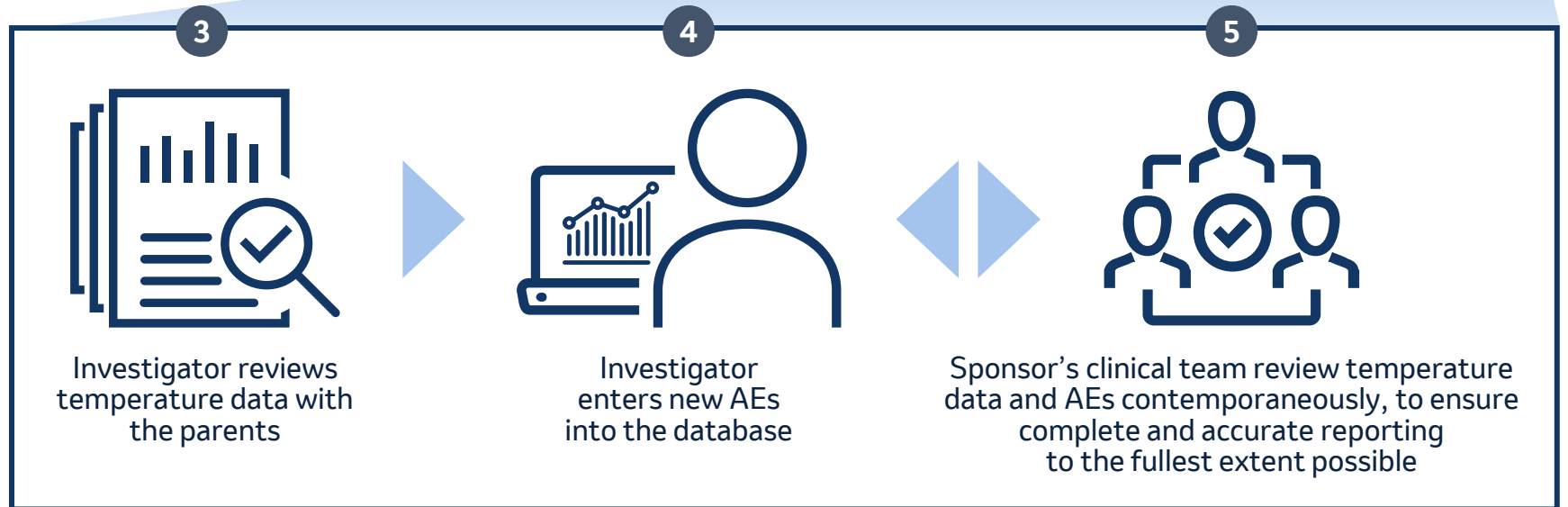
(If fever suspected)



1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15



Day of vaccination



# ISS: Maximum temperatures, by the Brighton Collaboration cut points, are comparable between the groups after each dose of PCV

	Infant Series												Toddler Dose			
	Dose 1				Dose 2				Dose 3				Dose 4			
	V114 (N = 3002)		PCV13 (N = 1467)		V114 (N = 2939)		PCV13 (N = 1414)		V114 (N = 2894)		PCV13 (N = 1374)		V114 (N = 2803)		PCV13 (N = 1312)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<b>Patients in population</b>	3002		1467		2939		1414		2894		1374		2803		1312	
Without temperature data (Day 1 through Day 7)	7	(0.2)	9	(0.6)	37	(1.3)	20	(1.4)	29	(1.0)	30	(2.2)	31	(1.1)	25	(1.9)
With temperature data (Day 1 through Day 7)	2995	(99.8)	1458	(99.4)	2902	(98.7)	1394	(98.6)	2865	(99.0)	1344	(97.8)	2772	(98.9)	1287	(98.1)
<b>Maximum temperature (rectal or rectal equivalent)</b>																
<100.4°F	1639	(54.7)	808	(55.4)	1656	(57.1)	761	(54.6)	1724	(60.2)	798	(59.4)	1742	(62.8)	822	(63.9)
≥100.4°F and <101.3°F	998	(33.3)	475	(32.6)	844	(29.1)	434	(31.1)	753	(26.3)	379	(28.2)	694	(25.0)	331	(25.7)
≥101.3°F and <102.2°F	300	(10.0)	138	(9.5)	305	(10.5)	131	(9.4)	273	(9.5)	123	(9.2)	230	(8.3)	93	(7.2)
≥102.2°F and <103.1°F	41	(1.4)	28	(1.9)	65	(2.2)	53	(3.8)	72	(2.5)	28	(2.1)	61	(2.2)	23	(1.8)
≥103.1°F and <104.0°F	13	(0.4)	9	(0.6)	26	(0.9)	11	(0.8)	28	(1.0)	13	(1.0)	26	(0.9)	15	(1.2)
≥104.0°F and <104.9°F	3	(0.1)	0	(0.0)	3	(0.1)	3	(0.2)	11	(0.4)	1	(0.1)	10	(0.4)	3	(0.2)
≥104.9°F and <105.8°F	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)	0	(0.0)	4	(0.1)	0	(0.0)
≥105.8°F	0	(0.0)	0	(0.0)	3	(0.1)	1	(0.1)	0	(0.0)	2	(0.1)	5	(0.2)	0	(0.0)

Percentages for the maximum temperature categories are calculated based on the number of participants with temperature data. Multiple occurrences of maximum temperature are counted only once (in same participant, in same vaccination phase). Non-rectal temperatures have been converted to rectal equivalent.

▲ n=19 (0.7%)      ▲ n=3 (0.2%)

ISS: Post toddler dose, the differences were small and not statistically significant between V114 and PCV13 with respect to the proportions of participants with maximum body temperatures  $\geq 104.0^{\circ}\text{F}$

Statistical Method	V114 n (%)	PCV13 n (%)	Difference in %V114 vs PCV13 Estimate (95% CI) <sup>a</sup>	p-value <sup>b</sup>
Fisher's exact test	N/A	N/A	N/A	0.105
Miettinen and Nurminen method				
Unstratified	19 (0.7)	3 (0.2)	0.5 (-0.0, 0.9)	0.068
Stratified, Cochran-Mantel-Haenszel weights			0.4 (-0.1, 0.8)	0.120
Stratified, equal weights			0.4 (-0.2, 1.0)	0.119
Stratified, sample size weights			0.3 (-0.4, 0.7)	0.324

<sup>a</sup> Estimated differences and CIs are calculated based on the specified statistical method.

<sup>b</sup> Two-sided p-value for the between-treatment difference in the proportion of participants with a maximum temperature  $\geq 104.0^{\circ}\text{F}$  ( $40.0^{\circ}\text{C}$ ).

For V114-027, only participants who were randomized to the complete dosing schedule of PCV13 (Group 1) or V114 (Group 5) are included.

CI=confidence interval; N/A=Not applicable.



ISS: Clinical outcomes in V114 recipients with body temperature  $\geq 104.0^{\circ}\text{F}$  post toddler dose ( $n=19$ ) did not demonstrate a new safety concern

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- **Review of adverse events following the toddler dose (PD4):**
  - No febrile convulsions
  - No vaccine-related SAEs
  - 13/19 had an AE of pyrexia reported by the investigator
    - All but 1 were **non-serious** AEs
    - Majority resolved within 3 days
    - A single **serious** AE of pyrexia was reported and assessed as **non-vaccine-related** by the investigator
- **Possible confounding factors:**
  - Underlying **infection** was suggested in **10 out of 19** based on a review of concurrent (-/+3 days) non-vaccine-related AEs
  - **Seasonality** was observed, with 15 out of 19 occurring during the influenza season
  - **9/19 occurred after day 4**, which may be reflective of co-administered vaccines

# Conclusion: No new safety concern was identified for V114 with respect to postvaccination body temperatures

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In participants with maximum body temperatures  $\geq 104.0^{\circ}\text{F}$  after the toddler dose (PD4) in the integrated analysis:

- The between-group differences **were small** and **not statistically significant** based on both weighted and unweighted analyses
- **No vaccine-related SAEs** or events of **febrile convulsion** were reported among the V114 recipients
- Maximum body temperatures may have been **confounded** by concomitant vaccination and underlying infection

As for all Merck vaccines, post-marketing safety surveillance of V114 via **routine pharmacovigilance** activities will be conducted to ensure the safety profile remains adequately characterized.



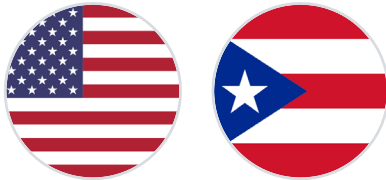
# Summary of Key Additional Analyses Submitted for V114 Pediatric US Filing

# FDA request for additional analyses based on concomitant administration of pentavalent combination vaccine

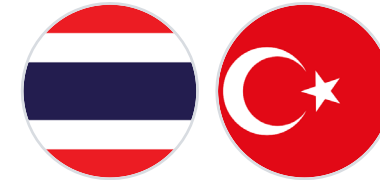


- V114-027 (interchangeability study) and V114-029 (3+1 pivotal study) included the co-administration of pentavalent combination vaccines

**Pentacel™ was used in  
US and Puerto Rico**



**Pentavac™ was used in Thailand and Turkey  
based on supply and certification requirements  
(Pentavac™ is not licensed in the US)**



**March 2022, FDA requested additional analyses for these studies including only participants who received Pentacel™ concomitantly (excluding participants who received Pentavac™)**

**The conclusions of the subgroup analysis (descriptive in nature) were largely unchanged from the original, despite the reduced sample size by ~30%**

# Results of the Pentacel™ subgroup are largely consistent with results of the overall study population

The **immunogenicity** and **safety** of V114 relative to PCV13 in the ad-hoc subgroup analysis limited to participants who received Pentacel™ as a concomitant vaccine are **consistent with the primary analysis** in the overall population



~30% reduction of the sample size led to a decrease in **power** for the MMR™II analysis at PD4 from **90% to 75%**



Narrow miss of the original prespecified NI margin (-5.4 vs -5) for **mumps** in the subgroup is not likely clinically significant

Response rates were high (>94%) in V114 recipients in the subgroup analysis

## Immunogenicity evaluations in Pentacel™ subgroup based on original protocol criteria

P029	P027
✓ NI met for all <b>15 serotypes</b> based on RR at PD3	✓ <b>Mixed PCV13/V114</b> regimens were <b>comparable</b> to a complete PCV13 regimen at PD4
✓ NI met for <b>14/15 serotypes</b> based on <b>IgG GMC at PD3</b> (narrowly missed ST 6a in both analyses)	✓ NI met for <b>RECOMBIVAX HB™</b> and <b>RotaTeq™</b> at PD3
✓ NI met for all 15 serotypes based on <b>IgG GMC at PD4</b>	
✓ NI met for <b>Pentacel™</b> at PD3	
✓ NI met for <b>VAQTA™, VARIVAX™, HIBERIX™, and MMR™II</b> for measles and rubella, >> <b>narrowly missed for mumps at PD4</b>	
✓ Superiority met for <b>ST3, 22F and 33F</b> at PD3 and PD4	
✓ <b>OPA</b> responses were <b>comparable</b> between the treatment groups	

NI: non-inferiority

# Conclusions

# Conclusions of the V114 pediatric clinical development program

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## In children with an unmet medical need for pneumococcal disease prevention:

- V114 is **well tolerated** with a safety profile that is consistent with licensed PCVs
- V114 induces **robust immune responses** to **13 serotypes shared** with PCV13 without significant loss of immunogenicity
- V114 is **superior** to PCV13 for **shared serotype 3**, the single most frequent serotype causing residual disease
- V114 is **superior** to PCV13 for **serotypes 22F and 33F**, which are of high public health importance
- V114 can be administered **concomitantly** with other routine pediatric vaccines

Therefore, V114 has the potential to significantly address the burden of remaining pneumococcal disease due to vaccine-types (including serotype 3) and leading non-vaccine types (serotypes 22F, 33F) in children.



Thank you.