

V114: An Investigational 15-Valent Pneumococcal Polysaccharide Conjugate Vaccine (PCV)

Key Results of the Adult Clinical Development Program

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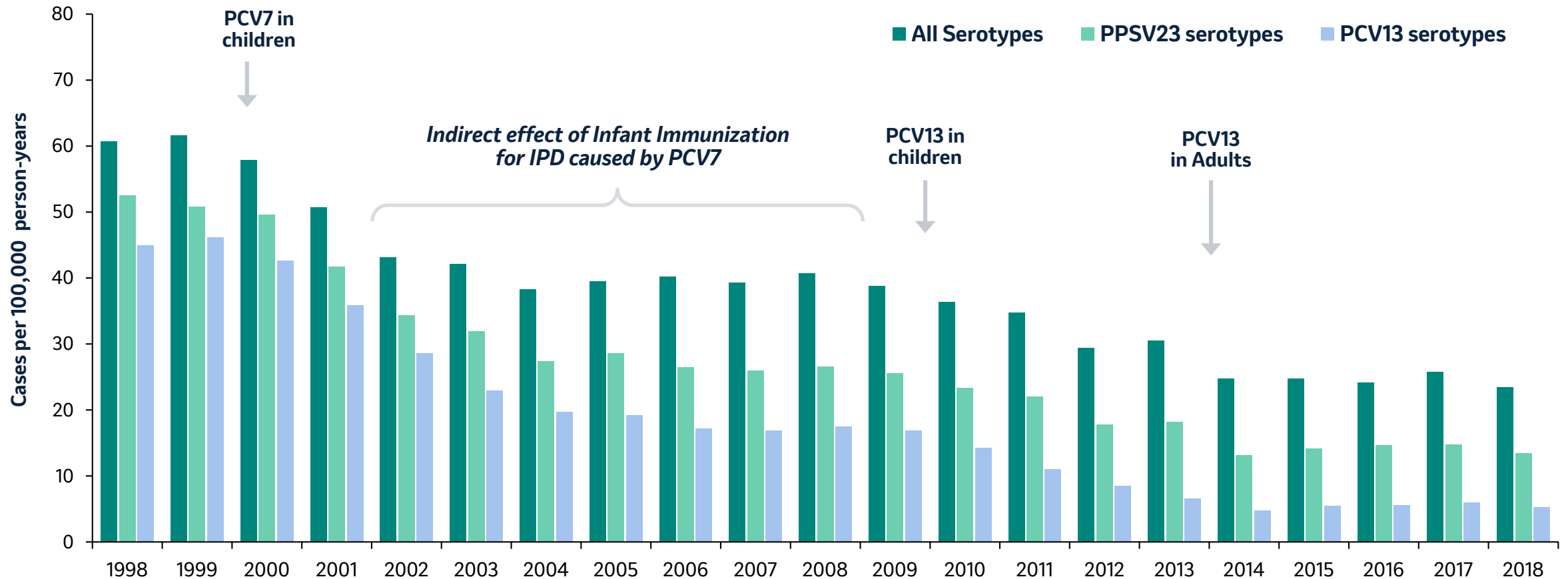
Presentation topics

- > **Rationale for the Development of V114**
- > **Overview of the Adult Clinical Development Program**
- > **Immunogenicity Results**
- > **Safety Results**
- > **Conclusion**
- > **Q&A**

Pediatric PCV vaccination has indirectly reduced adult invasive pneumococcal disease caused by vaccine serotypes in the US



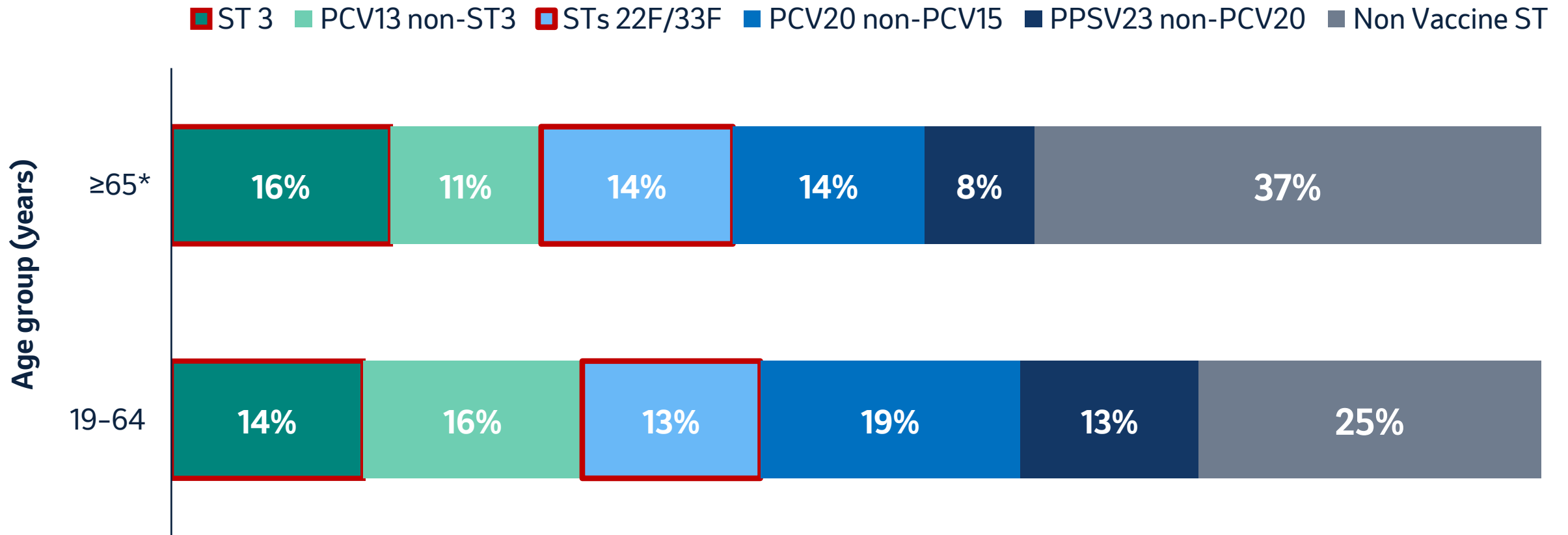
IPD incidence by serotypes, adults ≥65 years of age



Serotypes 3, 22F and 33F are major serotypes causing IPD in adults in the US



US Adults: Proportion of IPD caused by serotypes included pneumococcal vaccines, by age group (% IPD, 2017-2018)



*IPD Incidence in ≥ 65 years of age (2018): 24/100,000; incidence in age group 19-64 years not available

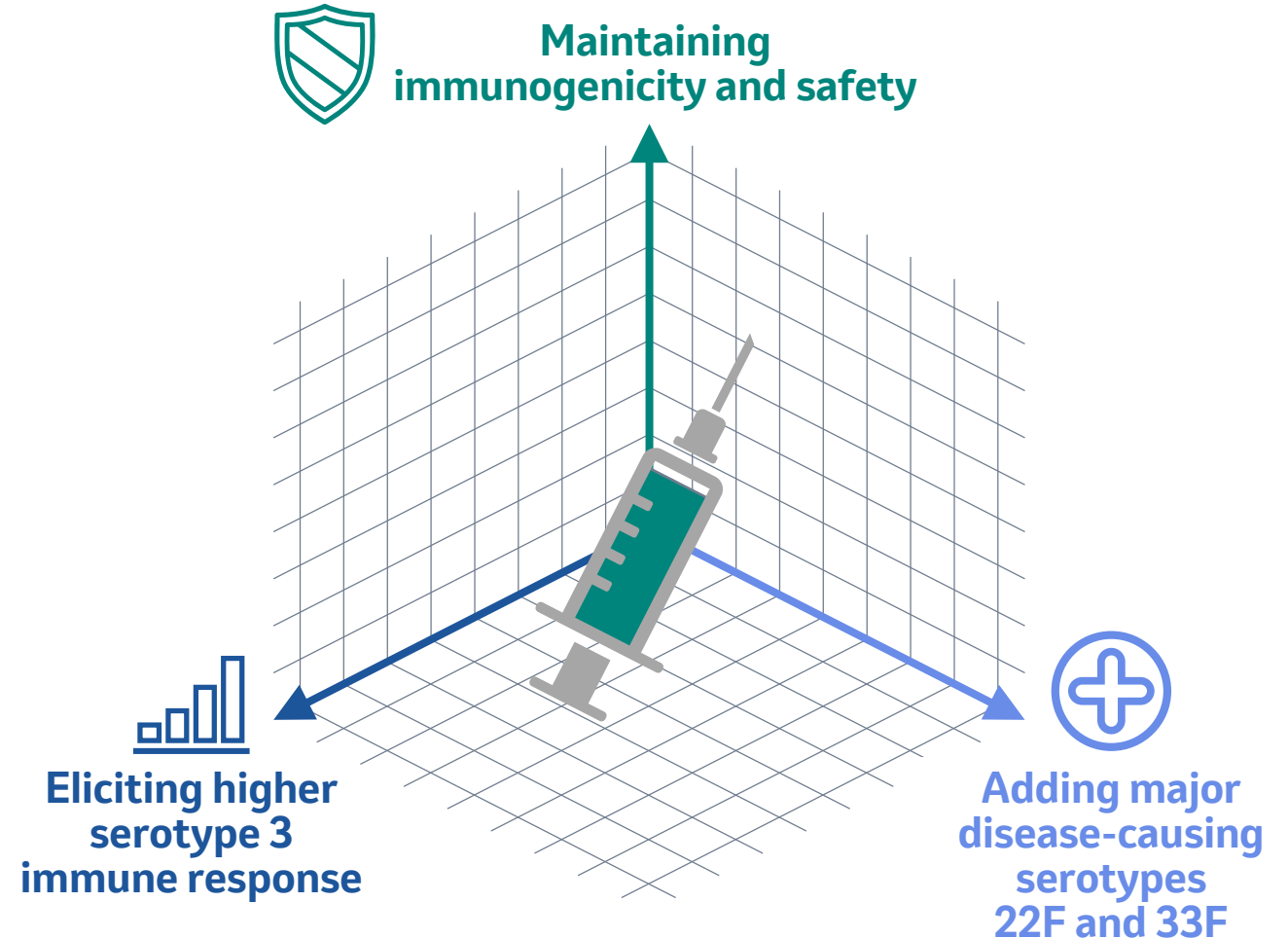
Pilishvili T., Gierke R., Farley M., et al "Epidemiology of Invasive Pneumococcal Disease (IPD) Following 18 years of Pneumococcal Conjugate Vaccine (PCV) use in the United States." International Symposium on Pneumococci and Pneumococcal Diseases June 21-24 2020, Toronto, Canada. Poster Presentation.

Rationale for the development of V114

Increase availability of PCVs worldwide

Develop single vaccine formulation for adult and pediatric indication to:

- **Maintain** robust immune responses to serotypes included in licensed PCVs
- **Extend** coverage to major non-vaccine serotypes
- **Improve** immunogenicity for serotype 3
- Demonstrate **comparable** safety profile to licensed PCVs



Targeted V114 US timelines

Population		Licensure
	 Adult¹	July 2021

Population		Filing
	 Pediatric²	2nd Half 2021

¹V114 adult US priority review

²V114 targeted pediatric US timeline dependent on approval of adult BLA

V114 Adult clinical program targets populations with an unmet medical need for pneumococcal disease prevention

Adults ≥ 50 Years of Age

Pivotal
(V114-019)

Lot-to-Lot Consistency
(V114-020)

Sequential with PPSV23
(V114-016)

Prior History of PPSV23
Ph. 2 (V114-007)

≥65 years of age

Concomitant Use

Concomitant influenza
(V114-
≥50 years of age

Adults 18-49 Years of Age

Immunocompetent
Increased Risk
(V114-017)

Special Populations

HIV
(V114-018)

HSCT-Adult, Ongoing
(V114-022)¹

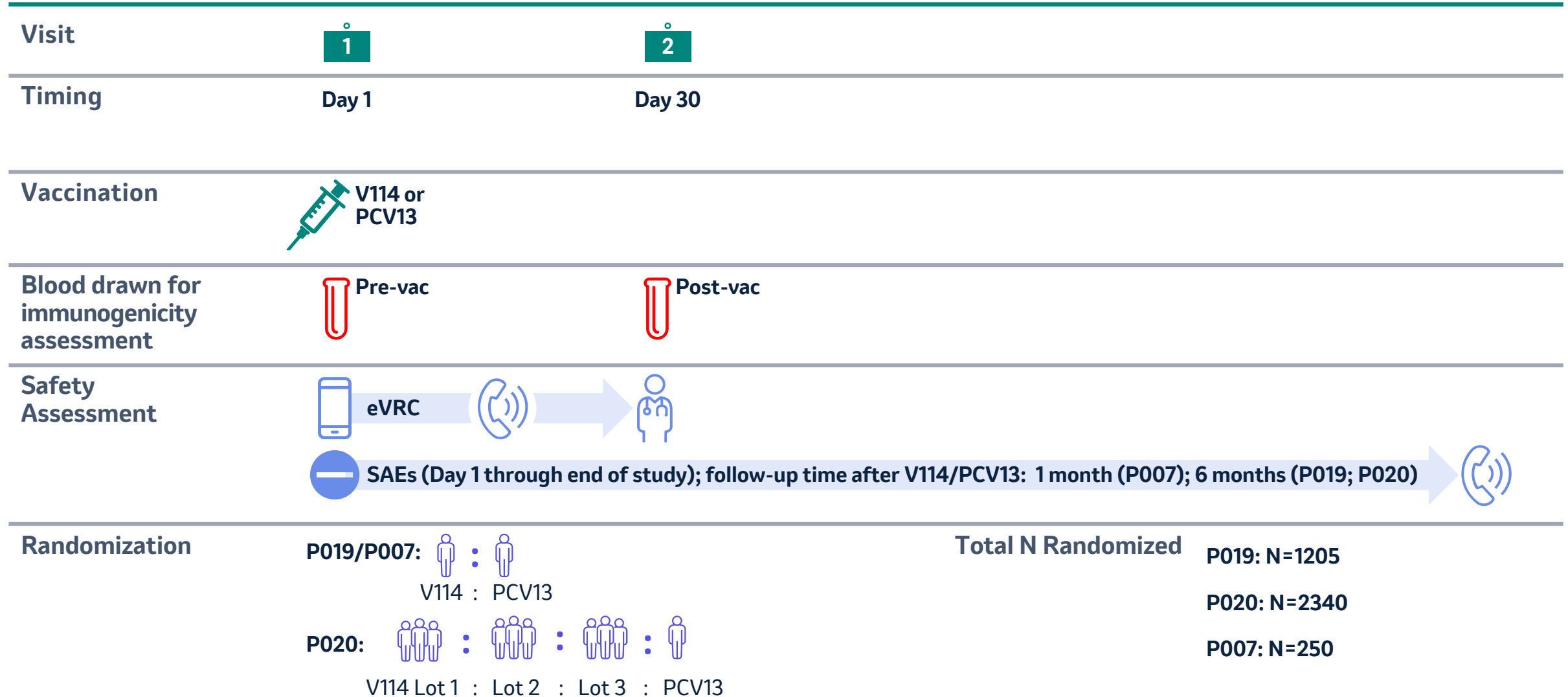
≥18 years of age

Studies with sequential vaccination PCV/PPSV23

HIV = Human Immunodeficiency Virus HSCT = hematopoietic stem cell transplant

¹ V114-022: Safety and immunogenicity of V114 in pediatric and adult recipients of allogeneic HSCT; study ongoing; not part of initial BLA.

Study design: Single dose V114 or PCV13 (V114-019; V114-020; V114-007)

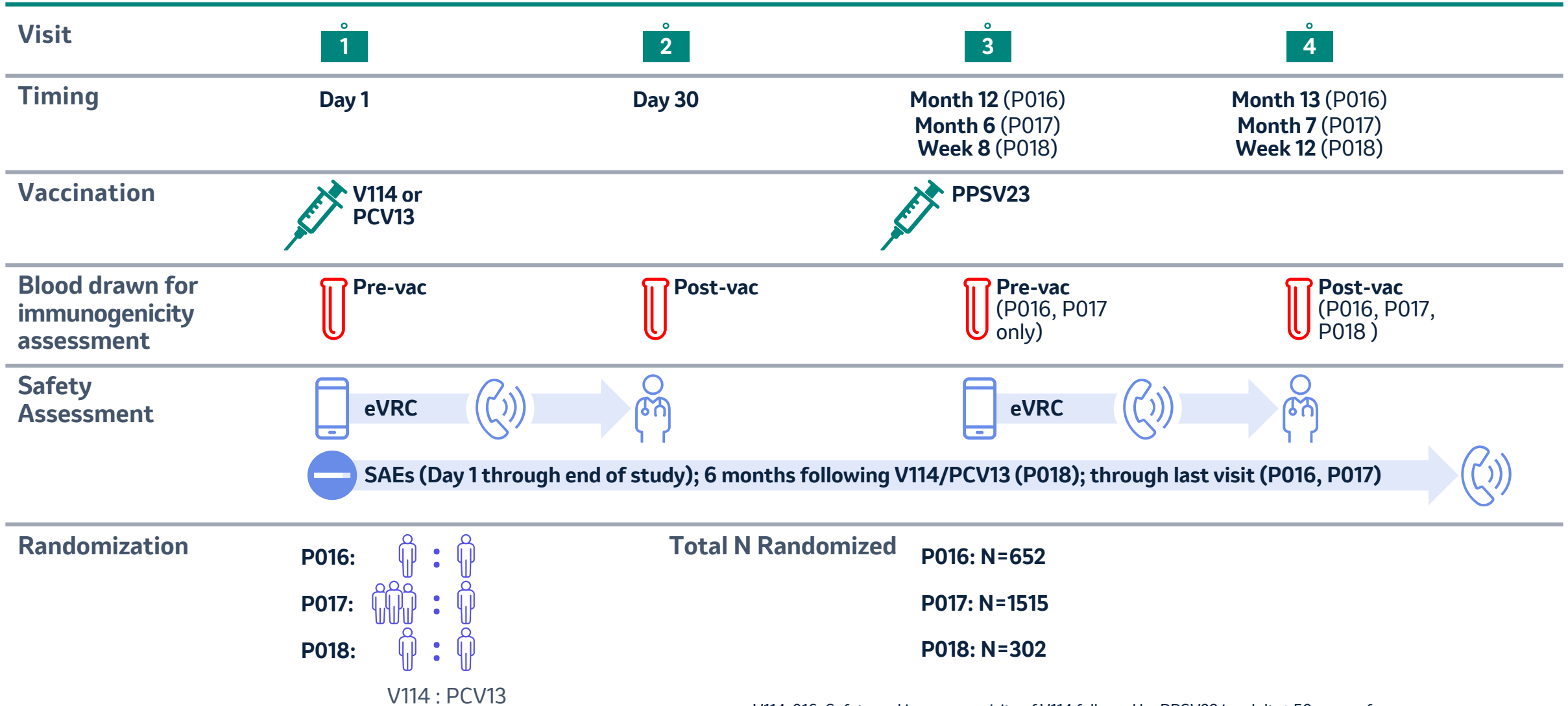


V114-019: Safety and immunogenicity of V114 in adults ≥50 years of age (pivotal).

V114-020: Lot-lot consistency of V114 in adults ≥50 years of age.

V114-007: Safety and immunogenicity of V114 in adults ≥65 years of age previously vaccinated with PPSV23.

Study design: Sequential vaccination with V114 or PCV13 followed by PPSV23 (V114-016; V114-017; V114-018)



V114-016: Safety and immunogenicity of V114 followed by PPSV23 in adults ≥50 years of age.
 V114-017: Safety and immunogenicity of V114 in adults 18–49 years of age at risk for pneumococcal disease.
 V114-018: Safety and immunogenicity of V114 in adults infected with HIV.

Immunogenicity results in adults 50 years of age and older (V114-019, 020 and 016)

V114-019: Safety and immunogenicity of V114 (pivotal)

V114-020: Lot-to-lot consistency of V114

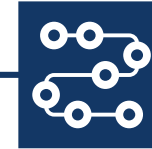
V114-016: Safety and immunogenicity of V114 followed by PPSV23

Immunogenicity evaluation and endpoints in the adult V114 program



Immunogenicity evaluation

- Serotype-specific immune responses to 15 serotypes in V114 were evaluated via:
 - Validated multiplex opsonophagocytic activity assay (MOPA) : functional opsonophagocytic antibodies (OPA)
 - Validated pneumococcal electrochemiluminescence (Pn ECL): IgG



Endpoints

- Serotype-specific OPA Geometric Mean Titers (GMTs) at 30 days postvaccination
- Geometric Mean Fold Rises (GMFRs) from prevaccination to postvaccination
- Proportions of participants with a ≥ 4 -fold rise in OPA titers from prevaccination to postvaccination
- Similar endpoints evaluated for IgG
- Reverse Cumulative Distribution Curves (RCDCs) display the distribution of OPA titers/IgG concentrations
- Generally, serotype-specific OPA GMTs as primary endpoints; IgG Geometric Mean Concentrations (GMCs) co-primary or key secondary endpoints

Serotype-specific OPA responses are the primary endpoint and accepted as basis for licensure
Immunogenicity analyses are based on the Per-Protocol population

V114-019 Pivotal study in adults ≥ 50 years of age: Objectives

Safety



To evaluate the safety and tolerability of V114

Immunogenicity



Primary

1

To demonstrate noninferiority of V114 to PCV13 for 13 shared serotypes

OPA GMTs (Day 30)

• 2-fold margin

To demonstrate superiority of V114 to PCV13 for the 2 unique serotypes (22F/33F)

OPA GMTs (Day 30)

• 2-fold margin AND

≥ 4 -fold rise in OPA response
(from Day 1 to Day 30)

• 10-percentage point difference in the proportions

Secondary

2

To demonstrate superiority of V114 to PCV13 for serotype 3

OPA GMTs (Day 30)

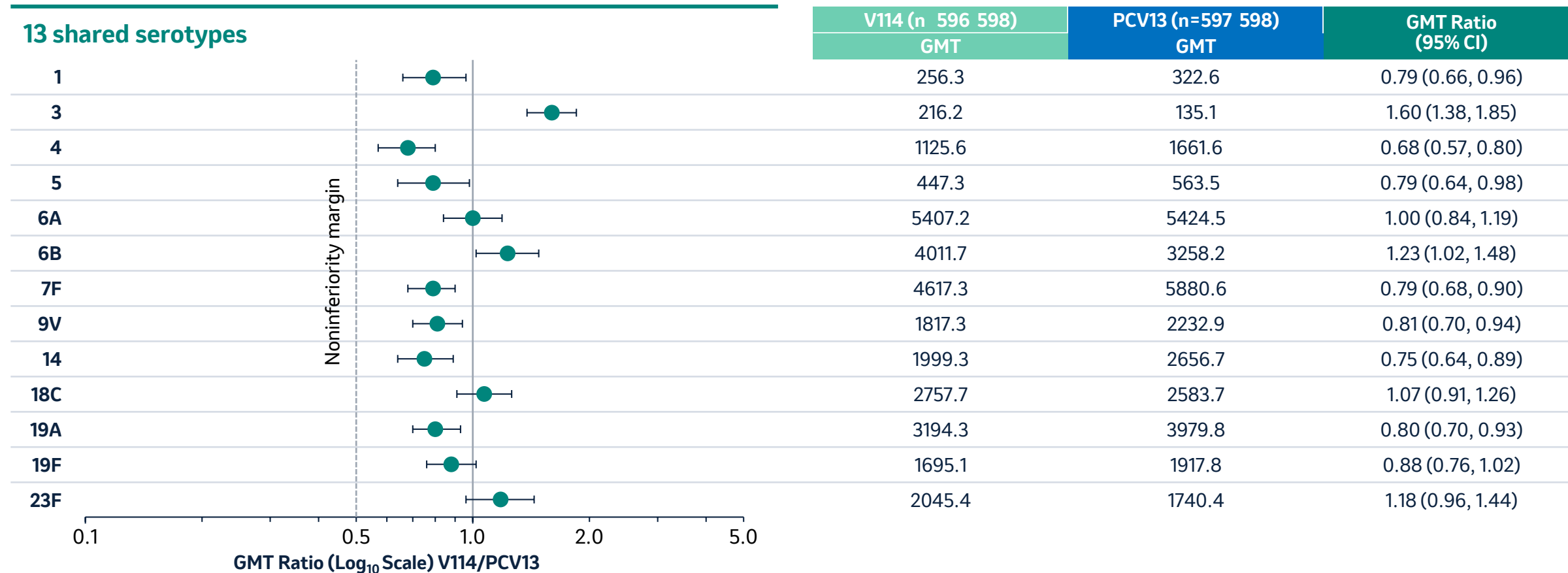
• 1.2-fold margin at Day 30 AND

≥ 4 -fold rise in OPA response
(from Day 1 to Day 30)

• 0-percentage point difference in the proportions

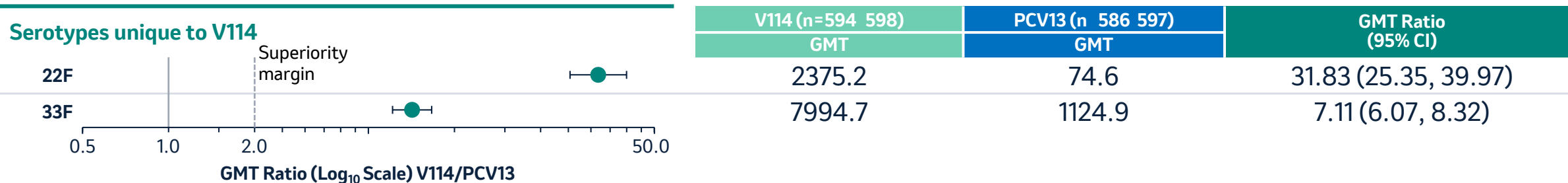
V114-019 (Pivotal study): V114 is noninferior to PCV13 for the 13 shared serotypes

OPA GMT ratios (Day 30)



V114-019 (Pivotal study): V114 is superior to PCV13 for 2 unique serotypes

OPA GMT ratios (Day 30)



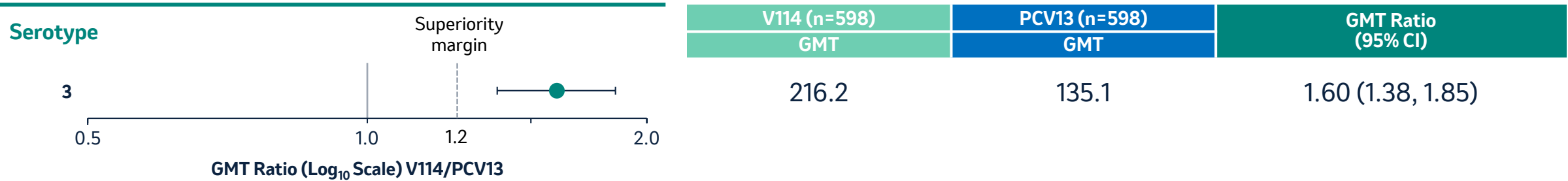
Proportions of subjects with a ≥ 4 -fold rise in OPA (Day 1 to Day 30)

Serotypes unique to V114	V114	PCV13	Percentage point difference (V114/PCV13)
	Observed response percentage (m/n)	Observed response percentage (m/n)	Estimate (95% CI)
22F	71.4 (374/524)	14.3 (71/498)	57.1 (52.0, 61.8)
33F	56.7 (328/578)	6.3 (35/560)	50.5 (45.9, 54.9)

V114-019 (Pivotal study): V114 is superior to PCV13 for serotype 3

(Key secondary immunogenicity objective)

OPA GMT ratio (Day 30)

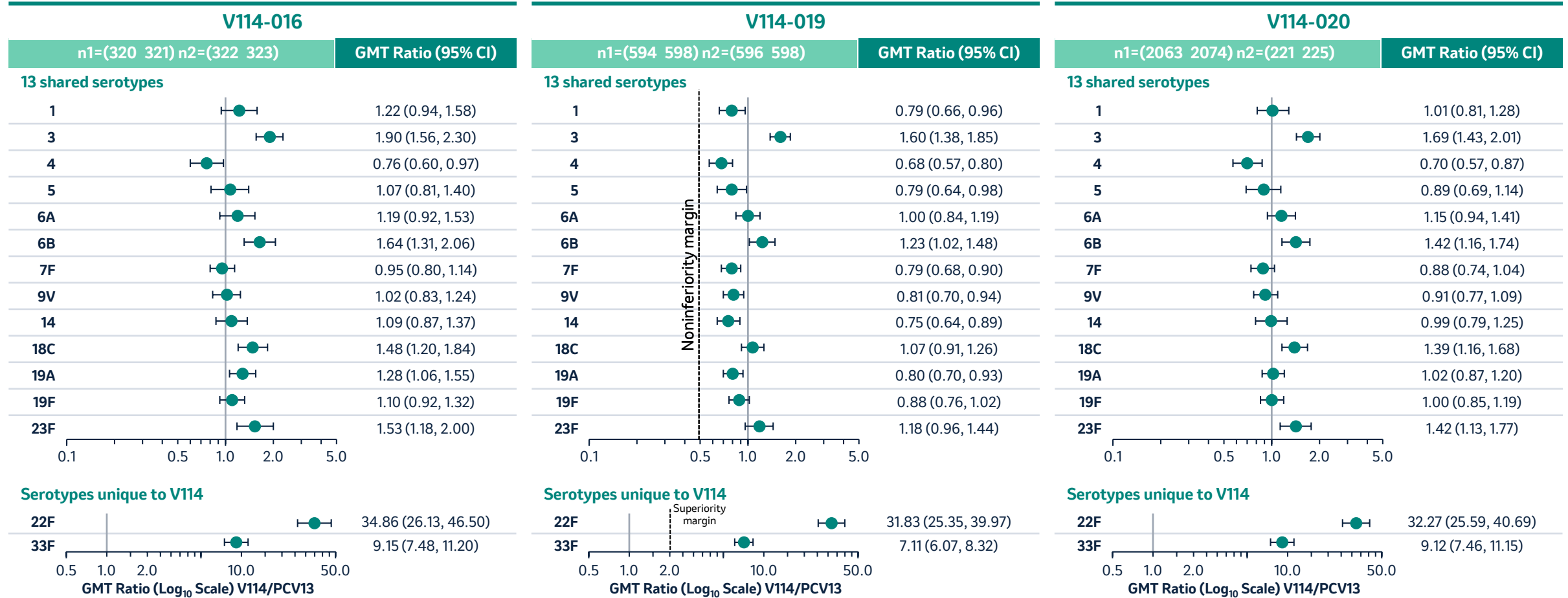


Proportions of subjects with a ≥4-fold rise in OPA (Day 1 to Day 30)

Serotype	V114	PCV13	Percentage point difference (V114/PCV13)
	Observed response percentage (m/n)	Observed response percentage (m/n)	Estimate (95% CI)
3	70.2 (407/580)	58.7 (338/756)	11.5 (6.0, 16.9)

V114 induces consistent OPA responses in adults ≥50 years of age: V114-016, V114-019 and V114-020

OPA GMT ratios (Day 30)



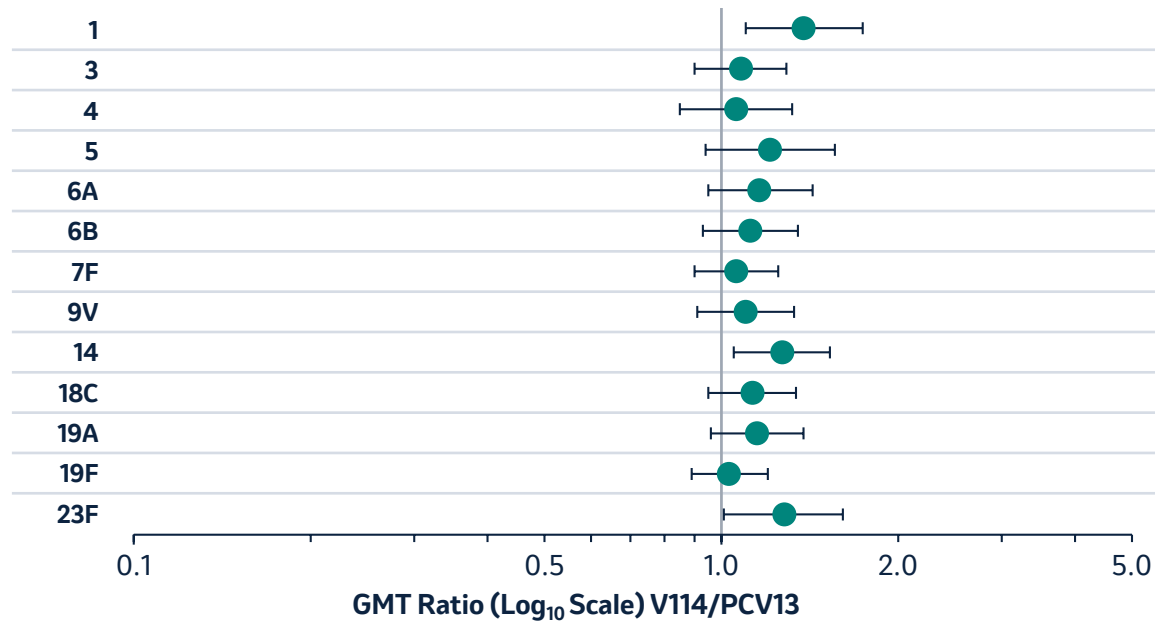
n1: V114 group
n2: PCV13 group

V114-016: Safety and immunogenicity of V114 followed by PPSV23 in adults ≥50 years of age.
V114-019: Safety and immunogenicity of V114 in adults ≥50 years of age (pivotal).
V114-020: Lot-to-lot consistency of V114 in adults ≥50 years of age.

V114-016 (Sequential): PPSV23 administered 12 months after V114 or PCV13 induces OPA responses that are comparable in both groups

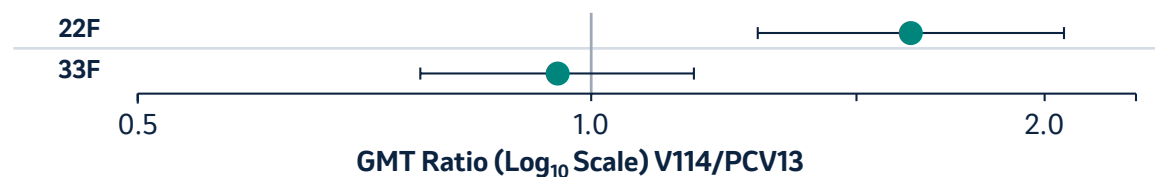
OPA GMT ratios (Month 13; 30 days following PPSV23)

13 shared serotypes



V114 (n=320 321)	PCV13 (n=322 323)	GMT Ratio (95% CI)
GMT	GMT	
392.2	283.2	1.38 (1.10, 1.74)
282.6	262.8	1.08 (0.90, 1.29)
1671.9	1580.4	1.06 (0.85, 1.32)
705.5	583.9	1.21 (0.94, 1.56)
3261.5	2806.8	1.16 (0.95, 1.43)
3223.9	2872.0	1.12 (0.93, 1.35)
5125.6	4848.0	1.06 (0.90, 1.25)
2059.5	1872.0	1.10 (0.91, 1.33)
3370.9	2660.5	1.27 (1.05, 1.53)
2379.6	2103.9	1.13 (0.95, 1.34)
3657.1	3170.8	1.15 (0.96, 1.38)
2229.7	2156.2	1.03 (0.89, 1.20)
1894.2	1485.1	1.28 (1.01, 1.61)

Serotypes unique to V114

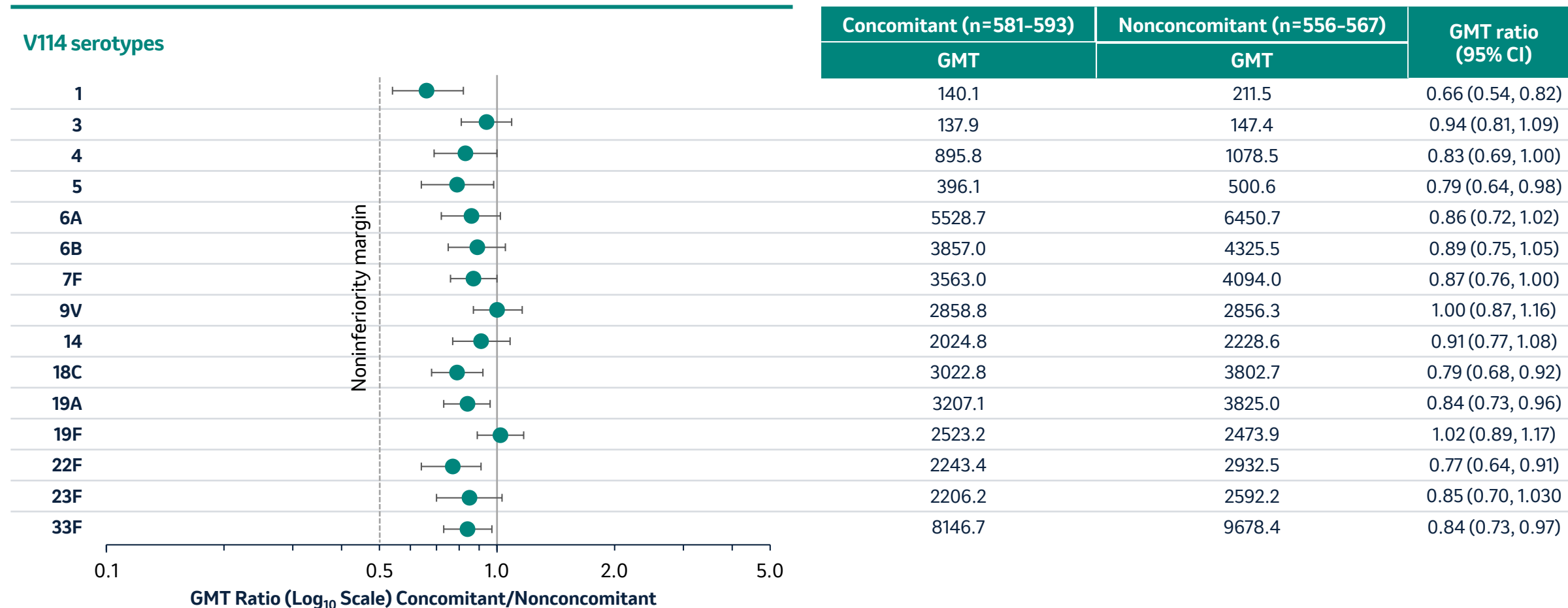


V114 (n=321)	PCV13 (n 323)	GMT Ratio (95% CI)
GMT	GMT	
3124.4	1921.6	1.63 (1.29, 2.06)
7881.6	8269.9	0.95 (0.77, 1.17)

Immunogenicity results with concomitant use of quadrivalent influenza vaccine (V114-021)

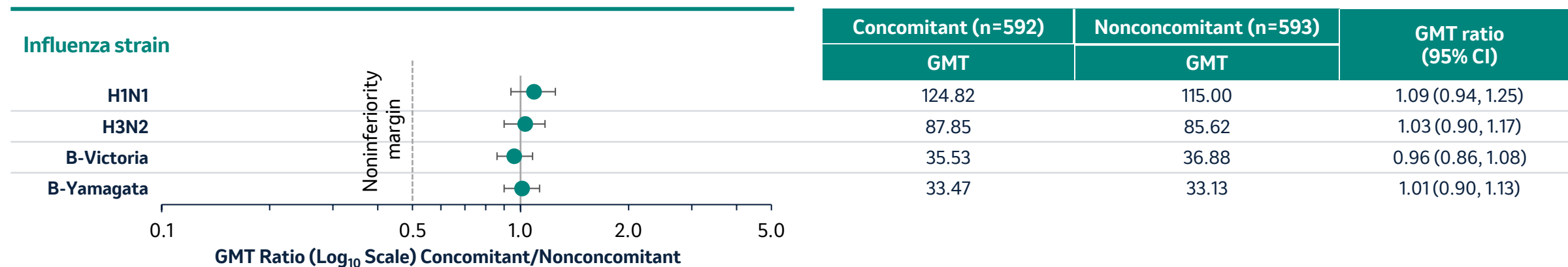
V114-021 (Influenza): Concomitant administration of V114 and quadrivalent influenza vaccine is noninferior to nonconcomitant administration (30 days apart)

OPA GMT ratios (Day 30 following V114)



V114-021 (Influenza): Concomitant administration of V114 and quadrivalent influenza vaccine is noninferior to nonconcomitant administration (30 days apart)

Hemagglutination Inhibition (HAI) GMT ratios (Day 30 following QIV)



Immunogenicity results in
immunocompetent adults
18–49 years of age with increased risk
for pneumococcal disease
(V114-017)

V114-017 (18–49 years of age): Baseline risk factors

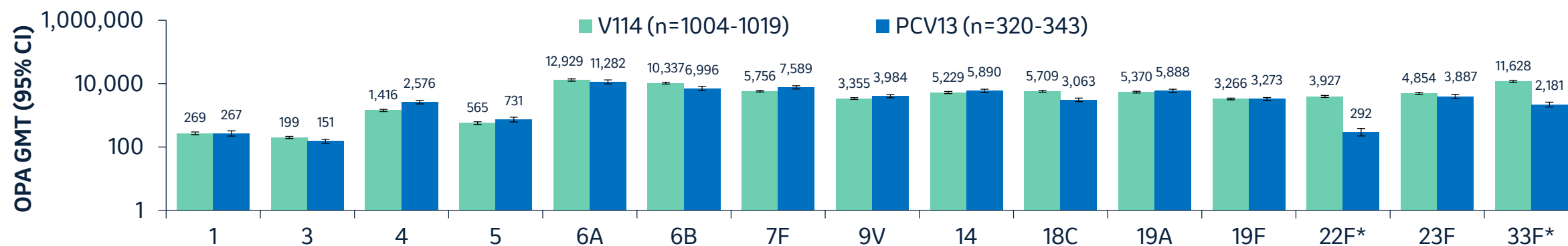
	V114 N=1133*	PCV13 N=379*
	n (%)	n (%)
Enrollment		
Center for American Indian Health	439 (38.7%)	148 (39.1%)
Risk factors		
No risk factors [‡]	285 (25.2%)	96 (25.3%)
Single risk factor	620 (54.7%)	207 (54.6%)
Chronic lung disease	163 (14.4%)	53 (14.0%)
Tobacco use	165 (14.6%)	56 (14.8%)
Diabetes mellitus	157 (13.9%)	51 (13.5%)
Chronic liver disease	28 (2.5%)	9 (2.4%)
Chronic heart disease	57 (5.0%)	20 (5.3%)
Alcohol consumption	50 (4.4%)	18 (4.7%)
Two or more risk factors	228 (20.1%)	76 (20.1%)

*Note: randomization in this study for V114 to PCV13 was 3:1

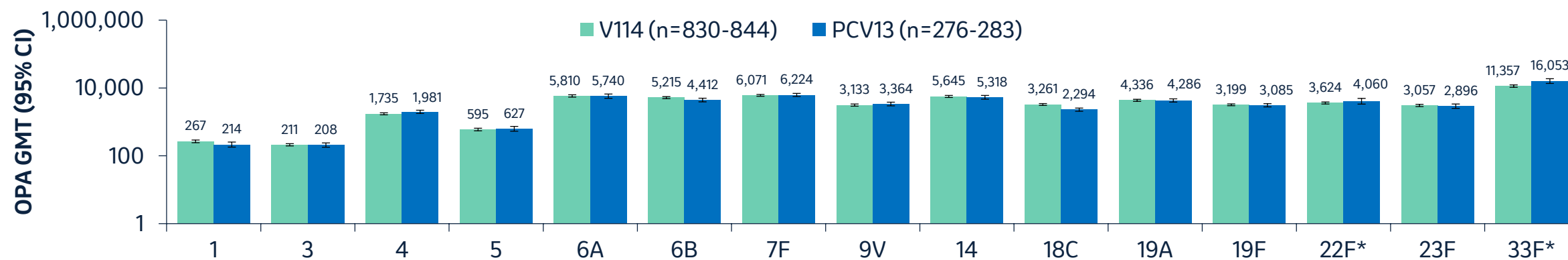
‡All participants with no risk factor and participants with single risk factor of increased alcohol consumption were enrolled at Center of American Indian Health sites.
V114-017: Safety and immunogenicity of V114 in adults 18–49 years of age at risk for pneumococcal disease.

V114-017 (18-49 years of age): V114 and sequential V114/PPSV23 are immunogenic for all 15 serotypes

OPA GMTs 30 days postvaccination with V114/PCV13 (Day 30)



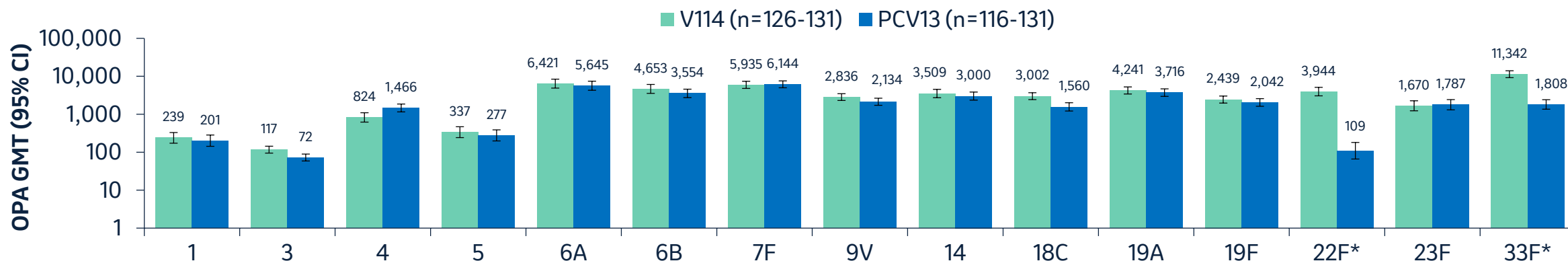
OPA GMTs 30 days postvaccination with PPSV23 (Month 7)



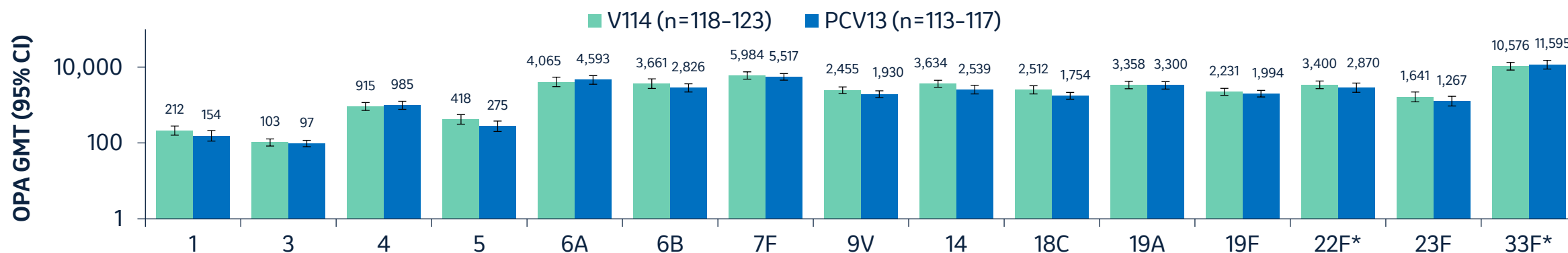
Immunogenicity results in adults living with HIV (V114-018)

V114-018 (HIV): V114 and sequential V114/PPSV23 are immunogenic for all 15 serotypes

OPA GMTs 30 days postvaccination with V114/PCV13 (Day 30)

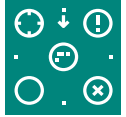


OPA GMTs 30 days postvaccination with PPSV23 (Week 12)



Serotype 3: Immunogenicity summary across adult V114 studies

No evidence of population-level impact of PCV 13 on serotype 3 burden

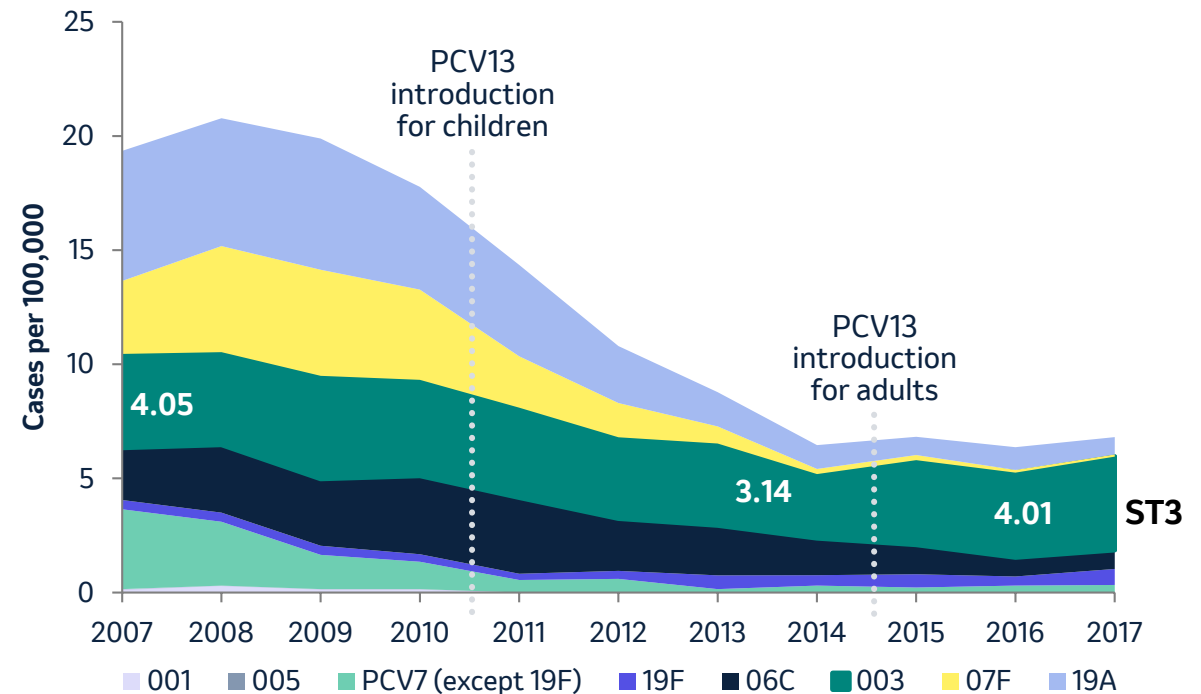


CDC/ACIP 2019 Position

- PCV13 may provide some level of direct protection against serotype 3 IPD and pneumonia
 - Inconsistent findings across studies and populations
 - Effectiveness is lower as compared to other PCV13-types
- No evidence of population-level impact on serotype 3 disease to date
 - Limited duration of protection
 - No impact on carriage = continued circulation and exposure of susceptible individuals
- Uncertainty remains on the expected benefits of PCV13 against serotype 3 disease

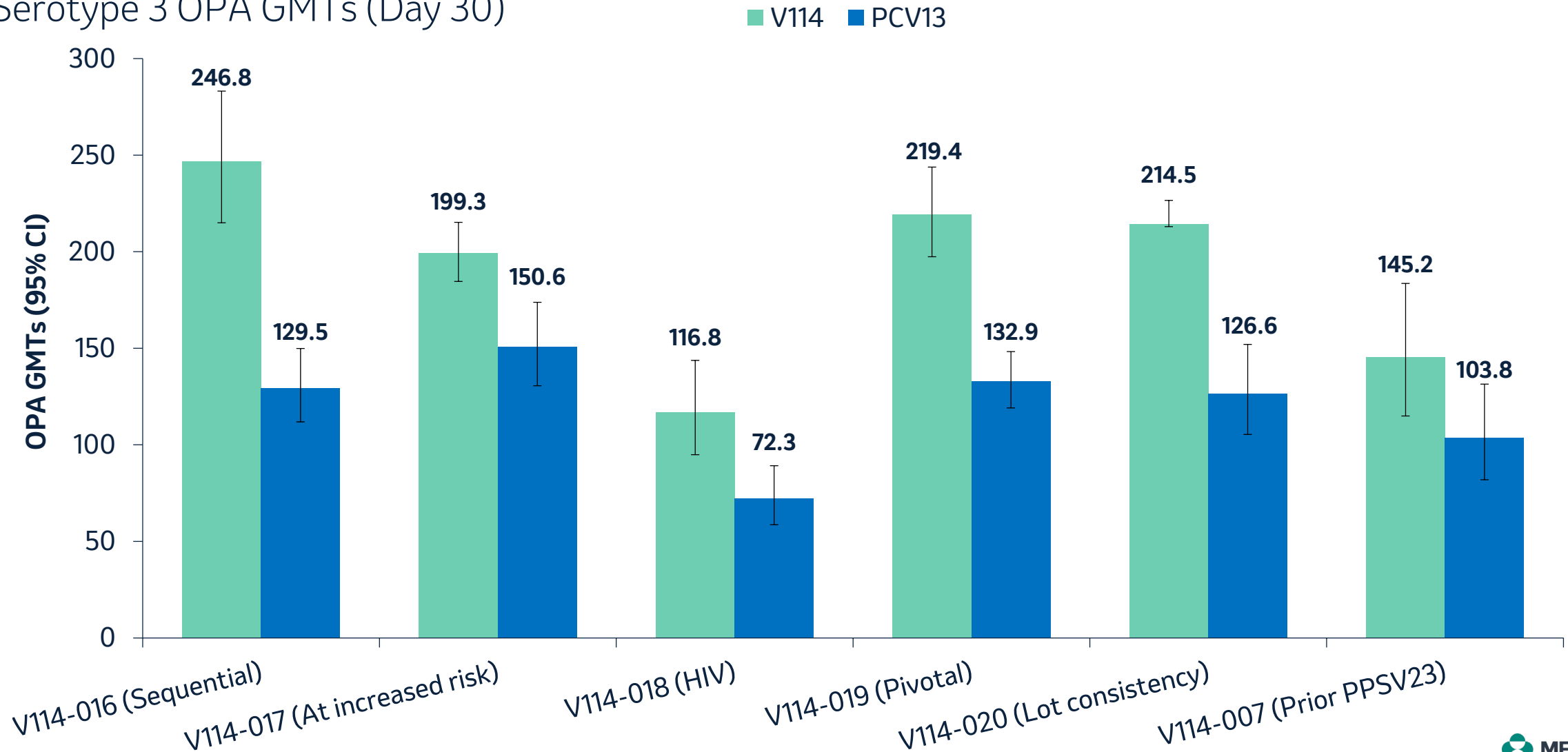


PCV13-type IPD rates ≥ 65 Years Old by serotype (2007-2017)



V114 induces robust OPA responses against serotype 3 in all adult studies

Serotype 3 OPA GMTs (Day 30)



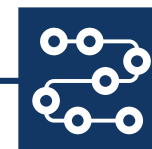
Safety results

Safety evaluation and endpoints in the V114 adult program



Safety evaluation

- Clinical review of adverse events (AEs) and postvaccination temperature measurements collected directly from study participants via a Vaccination Report Card



Safety endpoints

- Endpoints included the proportion of participants with:
 - Solicited injection-site AEs: erythema, swelling, and pain (Days 1-5 postvaccination)
 - Solicited systemic AEs: myalgia, arthralgia, headache, and fatigue (Days 1-14 postvaccination)
 - Any other injection-site or systemic AEs (Days 1-14 postvaccination)
 - Serious adverse events (≥ 6 months following V114)
 - Vaccine-related adverse events
 - Maximum temperature measurements (Days 1-5 postvaccination)

Safety analyses were based on the all participants as treated population which is defined as all randomized participants who received study vaccination

V114 Adult safety database



~7400 adults
≥18 years of age, of whom
~5600 received V114



Populations analyzed (7 studies)

- Adults **≥50 years of age**, pneumococcal vaccine-naïve (V114-016, V114-019, V114-020*)
- Adults (≥65 years of age) with **prior pneumococcal vaccine** administration (V114-007)
- Adults (≥50 years of age) administered **influenza vaccine concomitantly** and non-concomitantly (V114-021)
- Adults **18-49 years of age**, pneumococcal vaccine-naïve (V114-017)
- Adults (≥18 years of age) considered **immunocompromised** due to HIV infection (V114-018)

***Integrated Summary of Safety (ISS) Population:** Safety data following administration of PCV were pooled across 3 of the adult Phase 3 studies V114-016, V114-019, and V114-020 based on similarities in study population and design.

V114 is well tolerated in adults \geq 50 years of age with a safety profile generally comparable to PCV13

Summary of AEs

	Integrated Summary of Safety Population (V114-016, V114-019, V114-020)	
	V114 (N = 3032) Estimated % [†]	PCV13 (N = 1154) Estimated % [†]
With one or more AEs	72.3	62.2
Injection-site	63.7	51.4
Systemic	45.1	39.1
With vaccine-related AEs *	68.0	57.7
Systemic	34.6	29.2
With SAEs (within 6 months)	2.1	2.2
With vaccine-related SAEs	0.0	0.0
Who died	0.1	0.1

*Determined by the investigator to be related to the vaccine; all injection site AEs are assessed as vaccine-related per protocol

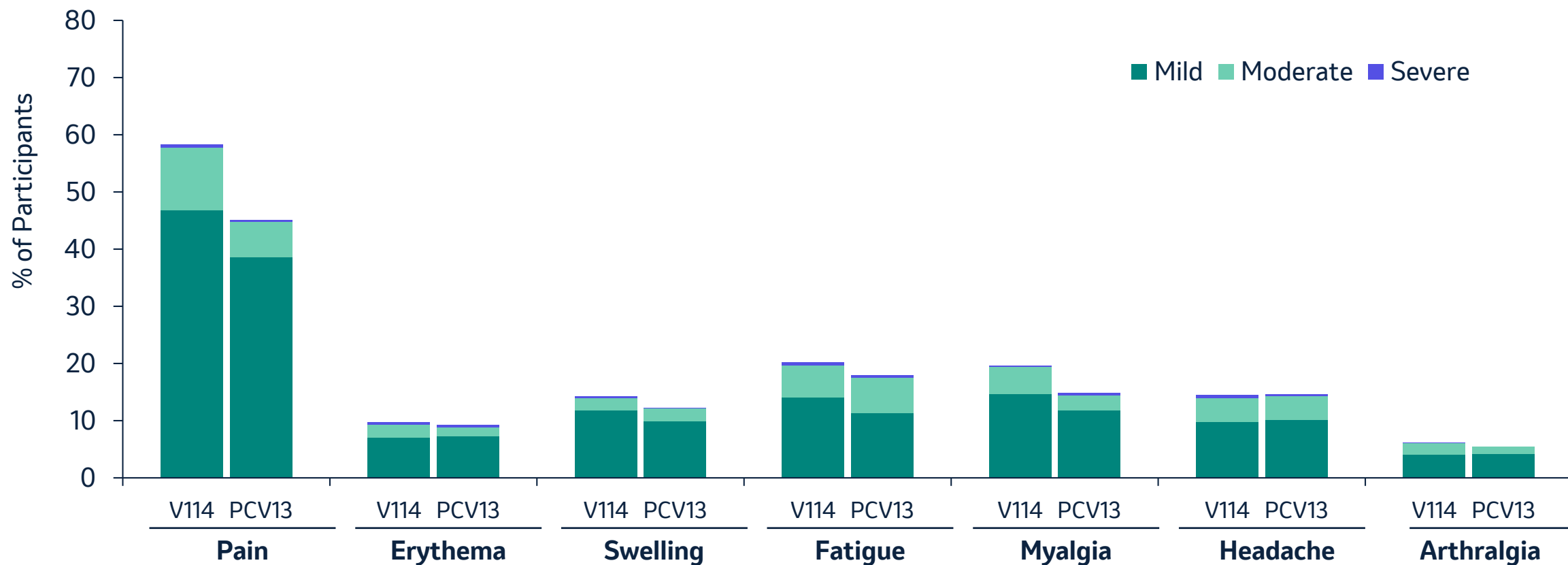
[†]The estimated % is a weighted average of the observed % in each study based on study size (across groups). Given the randomization ratio (9:1) and the higher proportions of participants reporting AEs across both vaccination groups in V114-020, the estimated differences may be smaller than the differences in the observed %s and are generally more consistent with the observed differences in each study.

V114-016: Safety and immunogenicity of V114 followed by PPSV23 in adults \geq 50 years of age. V114-019: Safety and immunogenicity of V114 in adults \geq 50 years of age (pivotal). V114-020: Lot-lot consistency of V114 in adults \geq 50 years of age.

V114 is well tolerated in adults ≥ 50 years of age with a safety profile generally comparable to PCV13

Frequency and severity of solicited AEs in the Integrated Summary of Safety Population

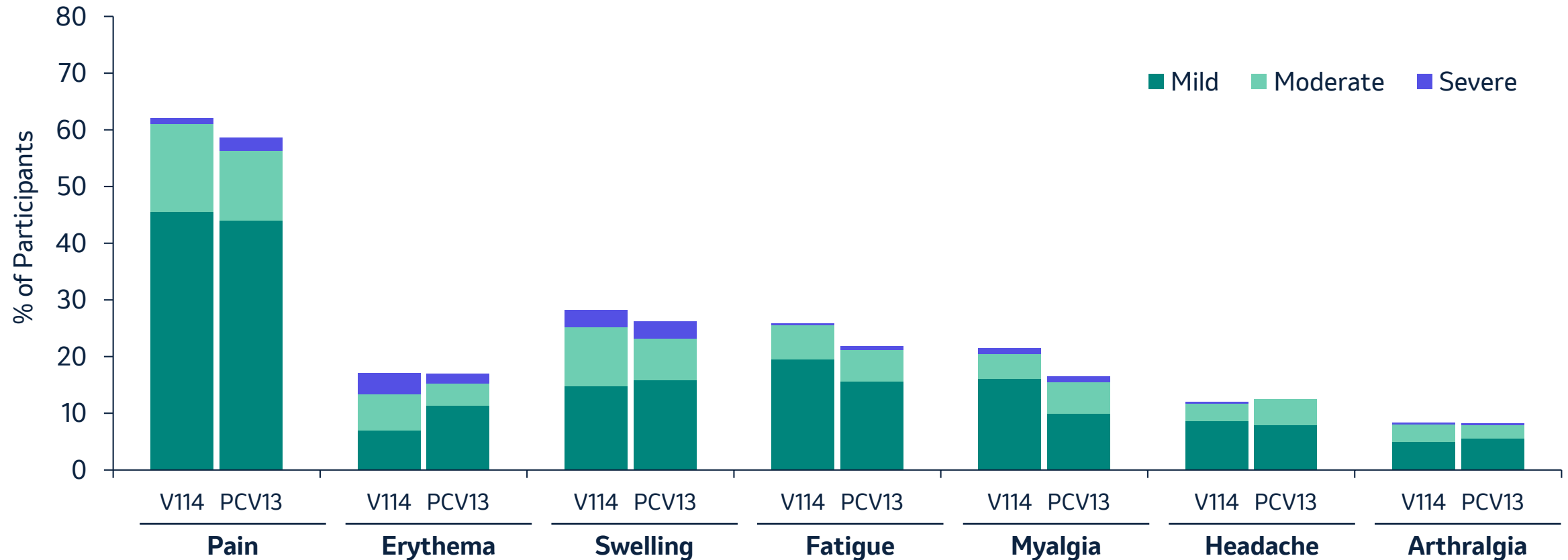
V114: N= 3032; **PCV13:** N=1154



V114-016 (Sequential): PPSV23 administered 12 months after V114 has a safety profile generally comparable to PPSV23 given after PCV13

Frequency and severity of solicited AEs following PPSV23 administration at Month 12

V114/PPSV23: N=298; PCV13/PPSV23: N=302



V114 is well tolerated in other key populations



Safety profile of V114 consistent with the safety profile in adults ≥ 50 years of age in:

- Immunocompetent adults 18–49 years of age at increased risk for pneumococcal disease
- Adults who receive concomitant seasonal influenza vaccine
- Adults ≥ 65 years of age who had previously received PPSV23 at least 1 year prior
- Adults living with HIV

Conclusions

Conclusions of the adult V114 clinical development program



In adults 18 years of age and older 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 **12 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 pneumococcal disease in adults
- V114 is **superior** to PCV13 for epidemiologically important **serotypes 22F and 33F**
- V114 can be followed sequentially by PPSV23 and administered concomitantly with influenza vaccine

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 adults.



Thank you
Q&A