9-valent HPV (9vHPV) Vaccine Program Design

ACIP

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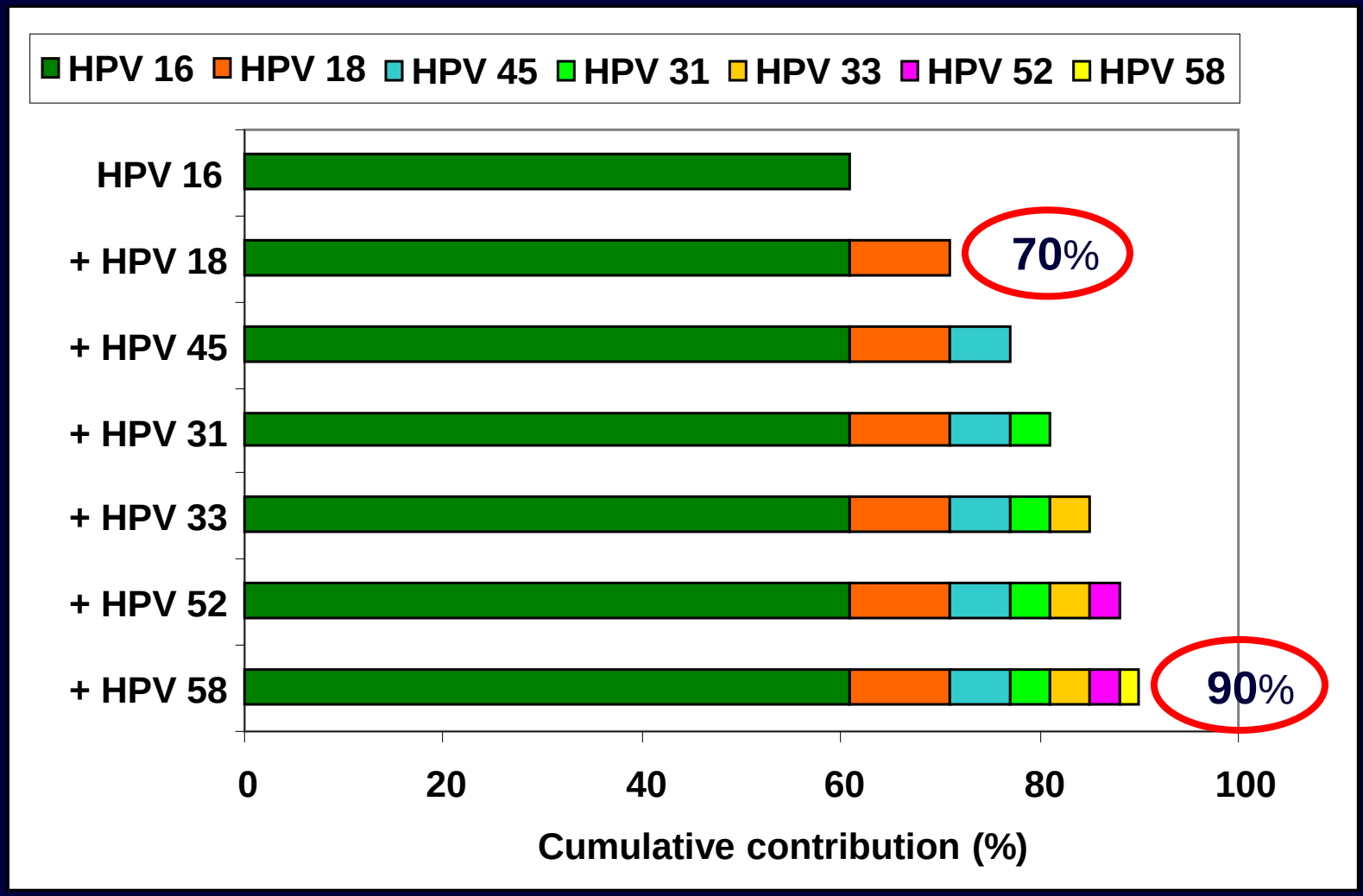
Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Cancers Worldwide



Based on de Sanjose et al. Lancet Oncol. 11:1048-56 (2010)

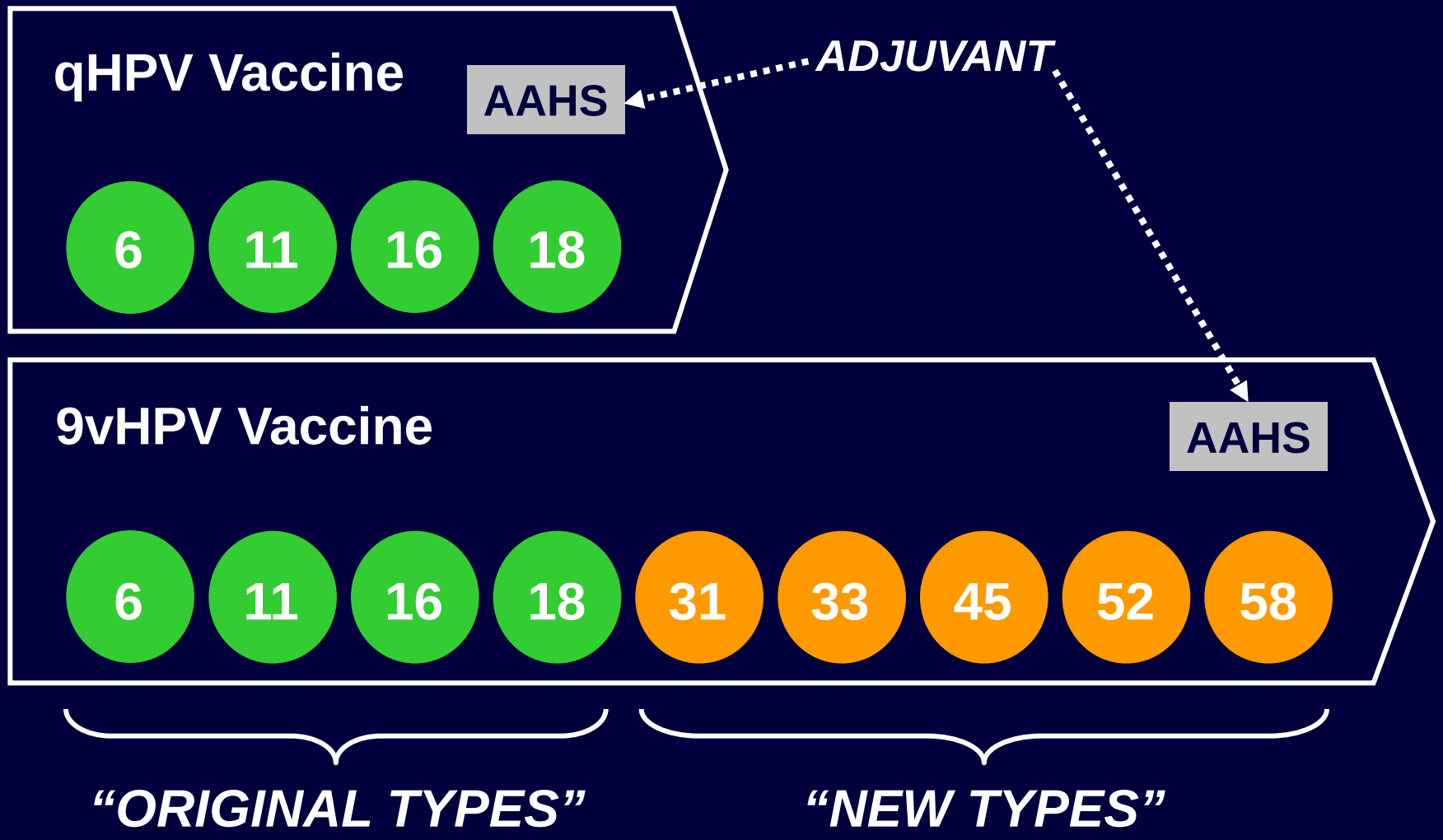
Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Disease

Type of lesion	6/11/16/18 Contribution	31/33/45/52/58 Contribution	Overall 9V Contribution
Cervical cancer*	70%	20%	90%
CIN2/3**	50%	30%	75-85%
CIN1**	30-35%	25%	50-60%

**Based on de Sanjose et al. 2010, Serrano et al. 2012*

***Based on the placebo cohort in the GARDASIL® clinical program & several meta analyses*

Comparison of qHPV Vaccine and 9vHPV Vaccine



Next Generation HPV Vaccine
Target Product Profile: 9vHPV Vaccine

Characteristic	Goal
Composition	HPV L1 VLP (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) AAHS adjuvant; 9-valent vaccine
Administration	3-dose regimen (Day 1, Month 2, Month 6); IM injection
Target age	9 to 26 years of age
Efficacy	Comparable to qHPV vaccine for the original HPV types Extension of efficacy (90% genital warts; ~90% cervical cancer) to additional high-risk HPV types
Safety / tolerability	Comparable to qHPV vaccine
Duration of protection	Comparable to qHPV vaccine

AAHS =Amorphous aluminum hydroxyphosphate sulfate

Key Goals of the 9vHPV Vaccine Clinical Program

Topic	Goal
Original HPV Types	Provide similar level of protection as qHPV vaccine against infection/disease due to original types
New HPV Types	Highly protective against infection/disease due to new types
Irrespective of HPV	Substantial protection against overall cervical/external genital disease, cytological abnormalities, and invasive procedures
Adolescents*	Non-inferior immunogenicity in adolescents vs. young women (immunobridging)
Safety	Acceptable safety/tolerability profile

**Adolescents cannot be directly assessed for efficacy (low exposure to HPV, constraints around performing genital examination in young adolescents)*

9vHPV Vaccine Studies for Initial Filing [1 of 2]: Pivotal Studies

Study	Population	N	Objective	Status
Pivotal efficacy study				
001	16-26 yo women	14000	Dose-ranging, efficacy, immunogenicity, safety	Completed Extension ongoing*
Immunobridging studies in adolescents				
002	9-15 yo boys & girls and 16-26 yo women	2800	Adult-to-adolescent immunobridging	Base study completed Extension ongoing*
009	9-15 yo girls	600	qHPV-to-9vHPV immunobridging	Completed
**Longer term safety, immunogenicity, efficacy/effectiveness*				

9vHPV Vaccine Studies for Initial Filing [2 of 2]: Supportive Studies

Study	Population	N	Objective	Status
Concomitant use studies				
005	11-15 yo boys & girls	1240	Concomitant use: Menactra*, Adacel**	Completed
007	11-15 yo boys & girls	1040	Concomitant use: Repevax***	Completed
Study in prior qHPV vaccine recipients				
006	12-26 yo girls & women	900	Safety in prior qHPV vaccine recipients	Completed

**Meningococal vaccine; **Tdap vaccine; ***Tdap/polio vaccine*

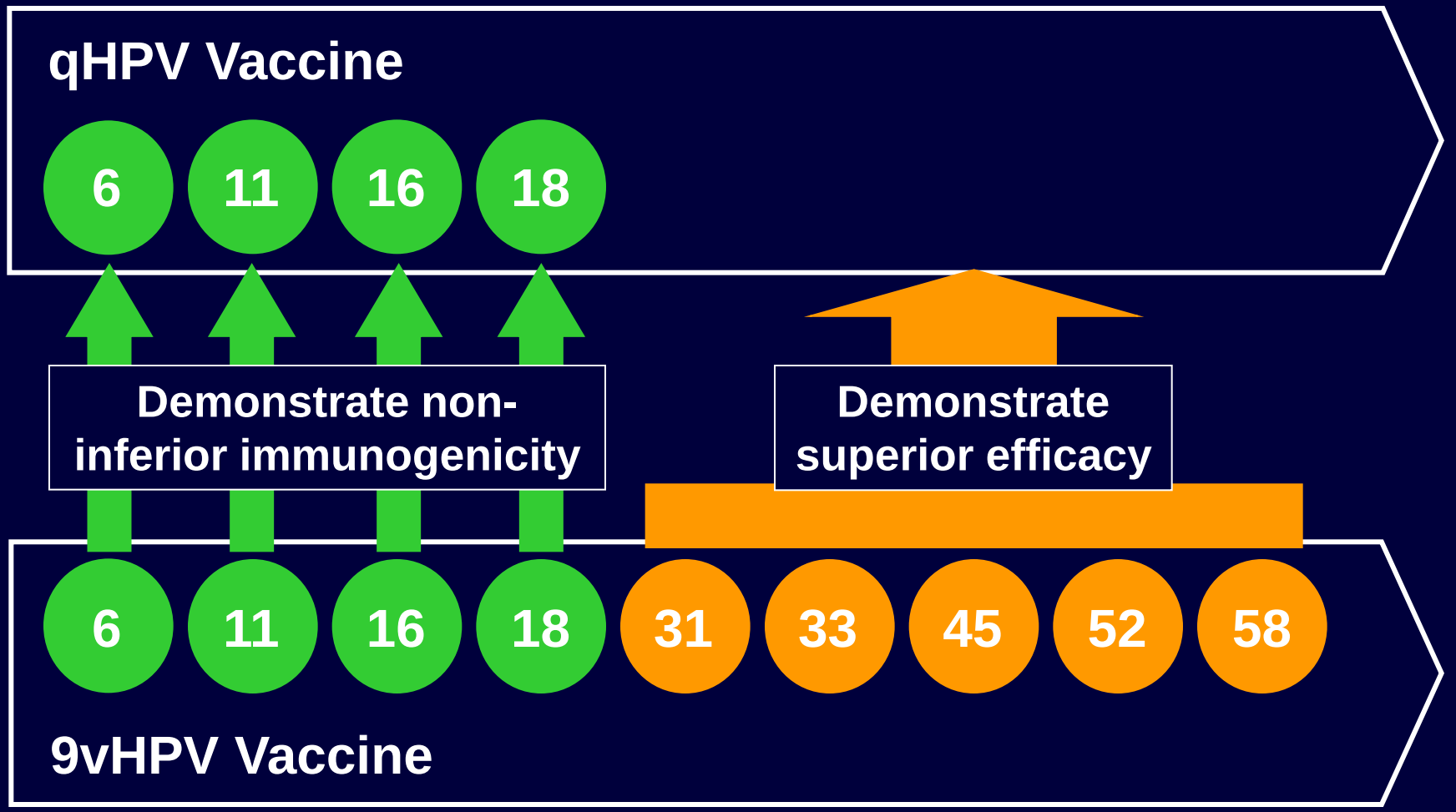
Development Considerations in the 9vHPV Vaccine Clinical Program

- **Cannot use placebo**
  - Ethical concerns
  - Active comparator (qHPV vaccine)

- **qHPV vaccine is highly efficacious**
  - No immune correlate for efficacy
  - Few disease endpoints expected in comparator cohort (cannot directly assess efficacy)

- **Strategy**
  - Bridge qHPV vaccine efficacy claims via demonstration of non-inferior immunogenicity (primary analysis)
  - Compare efficacy to historic placebo cohorts and demonstrate no negative trend in efficacy (supportive analysis)

Study 001: Primary Objectives (Pivotal Efficacy Trial)

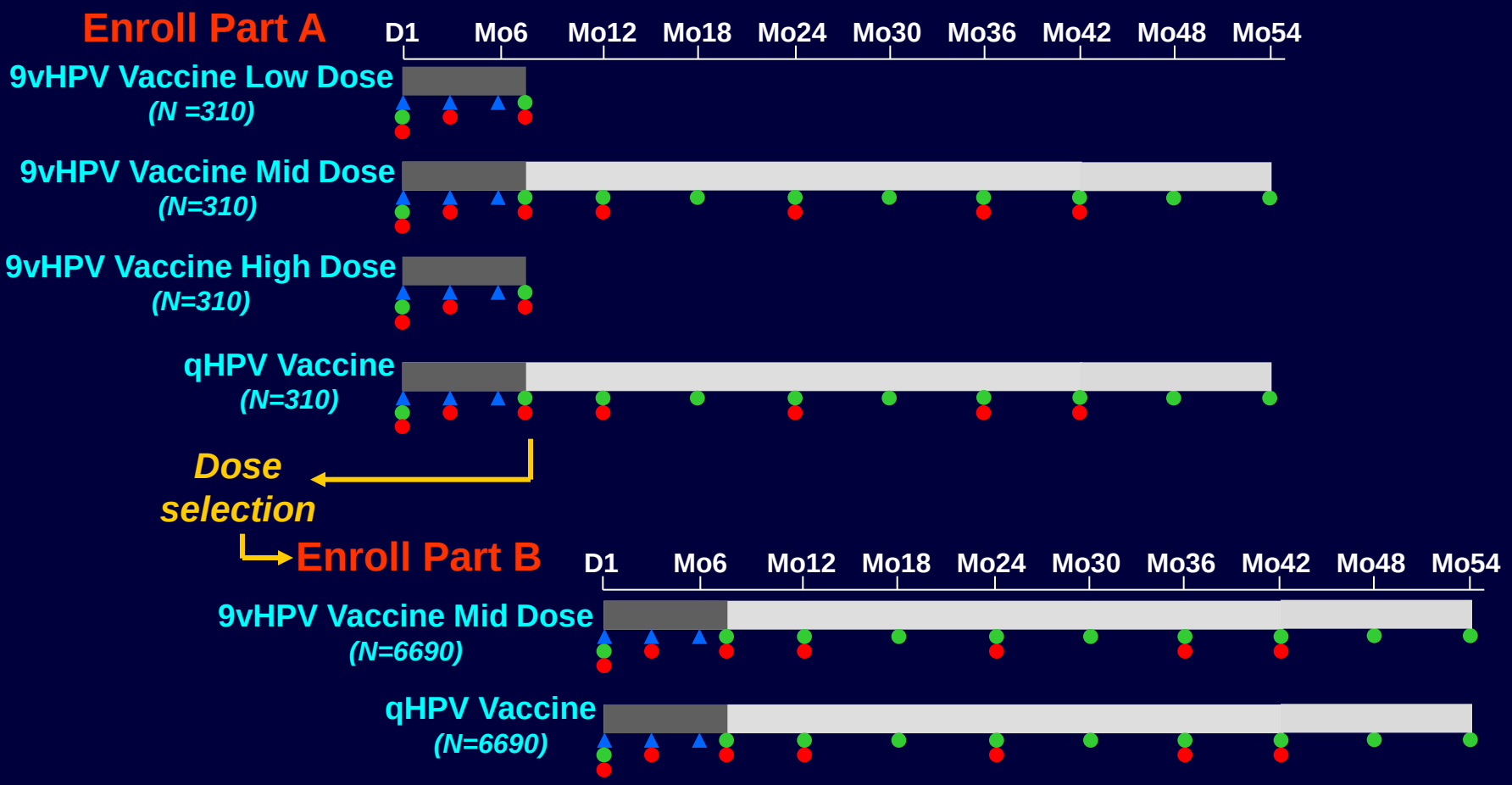


Study 001: Key Efficacy Objectives (Pivotal Efficacy Trial)

Objective category		Key objectives
ORIGINAL TYPES	*Primary*	Non-inferior immunogenicity 9vHPV vs. qHPV vaccine
	Exploratory	Incidence of 6/11/16/18-related persistent infection & disease*
NEW TYPES	*Primary*	Reduction of combined incidence of 31/33/45/52/58-related CIN 2/3+, VIN 2/3+, VaIN 2/3+**
	Secondary/ Exploratory	Reduction of incidence of 31/33/45/52/58-related • Cervical, vulvar, vaginal disease (any grade) • 6-month and 12-month persistent infection • Pap test abnormalities
IRRESPECTIVE OF HPV	*Secondary/ Exploratory*	Impact of 9vHPV vaccine on overall • Cervical, vulvar and vaginal disease* • Pap test abnormalities* • Cervical & external genital procedures*

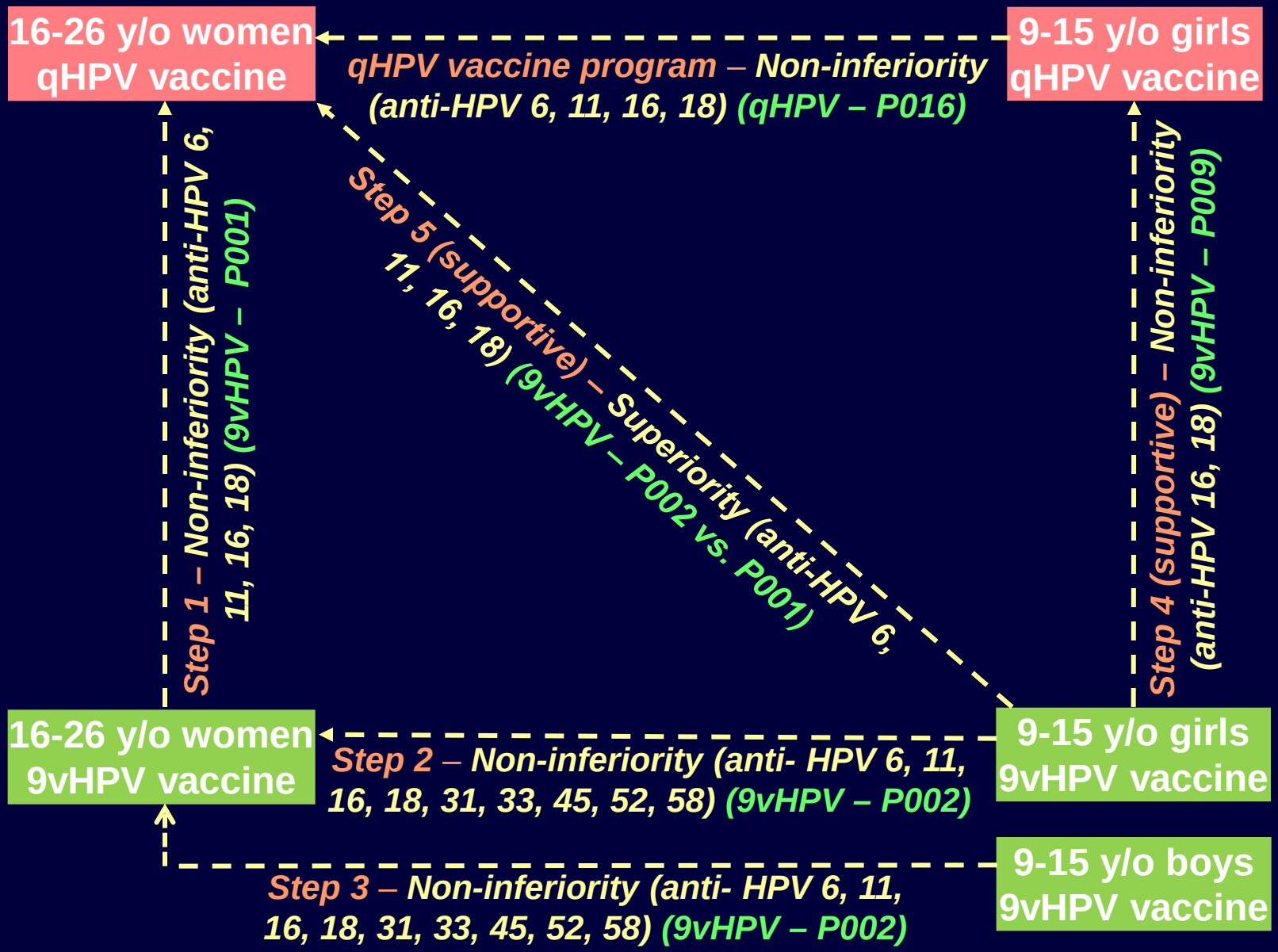
**Includes comparison with historic placebo arm of qHPV vaccine studies*
***Basis for licensure/cancer efficacy similar to that of qHPV vaccine*
Study population: 16-26 y/o females
Analysis populations: same as in the qHPV vaccine clinical program

Study 001: Study Flowchart (Pivotal Efficacy Trial)



** After 30 primary efficacy cases accrued, Mo48 and Mo54 visits not yet conducted were cancelled*

9vHPV Vaccine Program Immunobridging Strategy



Safety Assessment

- **Safety database**
  - ~13,300 subjects administered 9vHPV vaccine
    - ~8,000 young women, 16 to 26 years of age
    - ~5,300 adolescent girls and boys, 9 to 15 years of age
  - Database size similar to that for initial licensure of qHPV vaccine
- **Surveillance Methods for Safety Evaluation**
  - Similar to those use for licensure of qHPV vaccine
    - Elevated temperatures
    - Injection-site and systemic adverse experiences
    - Systemic adverse experiences regardless of causality D1 to Mo12 (or D1 to end-of-study for studies of less than 12-month duration)
    - Vaccine-related systemic adverse experiences and deaths (entire study period)
    - New medical history

Summary

- **Broaden cervical cancer and precancer coverage**
  - 9-valent HPV vaccine
    - 4 HPV types addressed by qHPV vaccine
    - 5 new cancer-causing HPV types
  - Potential to prevent
    - ~90% cervical cancers
    - ~80% high-grade cervical disease (CIN 2 or worse)
- **Comprehensive clinical development program**
  - Six completed Phase III studies
    - One pivotal efficacy study in women, 16 to 26 years of age
    - Two immunobridging studies in adolescents
    - Two concomitant use studies
    - Safety study in prior qHPV vaccine recipients
  - First presentation of results in the near future
    - EUROGIN conference (Nov. 2013)