Cell Culture Inactivated Influenza Virus Vaccine (ccIIV) Clinical Trial and Product Overview

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Presentation Overview

- Rationale for the Novartis cell culture inactivated influenza virus vaccine (ccIIV) program
- Review of ccIIV
  - Product characteristics
  - Overview of clinical trials
  - Summary of clinical data
  - Phase III data (brief review)
    - Immunogenicity
    - Efficacy
    - Safety & tolerability

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The Rationale for the Novartis ccIIV Program

- A cell-culture based influenza vaccine has been recognized as an unmet public health need [1]
- Cell-culture derived vaccine provides important redundancy to a production method that relies on a vulnerable avian species
- Cell culture offers an alternative growth medium for viruses that replicate poorly in egg systems

1. Cell culture as a substrate for the production of influenza vaccines: memorandum from a WHO meeting. *Bull World Health Organ.* 1995;73(4):431-435.

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ccIIV Product Characteristics

- Description
  - Subunit (purified surface antigen) influenza virus vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK 33016) cells
  - Contains no preservatives or antibiotics
  - Supplied as a single 0.5ml dose in a pre-filled syringe
- Proposed Indications and Usage
  - Active immunization for the prevention of influenza disease caused by influenza virus types A and type B contained in the vaccine in persons 18 years of age and older
- Administration
  - Intramuscular injection preferably in the region of the deltoid muscle of the upper arm

Summary of ccIIV Clinical Trials
(More than 6700 Doses Have Been Administered to Adults)

Study	Year/ Location	Age group	Phase	Comparator	Objectives
V58P1 V58P2	2002/03 Germany(P1); NZ(P2)	18-40 years (P1) 18+ years (P1& P2)	I/II	Agriflu	•Exploratory safety and tolerability studies •Immunogenicity
V58P4	2004/05 Poland	18+ years	III	Agriflu	•Immunogenicity •Safety and tolerability •Non-inferiority to egg-derived vaccine (secondary)
V58P4E1	2005/06 Poland	18+ years	III	Agriflu	•Immunogenicity in subjects who received cell-culture vaccine during prior year (extension of V58P4) •Safety and tolerability
V58P5	2005/06 US	18-49 years	II	Fluvirin	•Non-inferiority to egg-derived vaccine •Immunogenicity, safety and tolerability (secondary)
V58P9	2005/06 Lithuania	18-60 years	III	Agriflu	•Immunogenicity (lot to lot consistency) •Safety and tolerability •Long-term immunogenicity at 6 months (secondary)
V58P13	2007/08 US/Finland/ Poland	18-49 years	III	Placebo	•Efficacy compared to placebo against vaccine strains, non-vaccine, and all strains (secondary) •Immunogenicity, safety and tolerability (secondary)

Summary of ccIIV Clinical Data in Adults

Immunogenicity

- ccIIV-induced immune responses exceeded US CBER criteria against all tested strains
- Responses were non-inferior to a conventional egg-derived TIV at 21 days

Efficacy

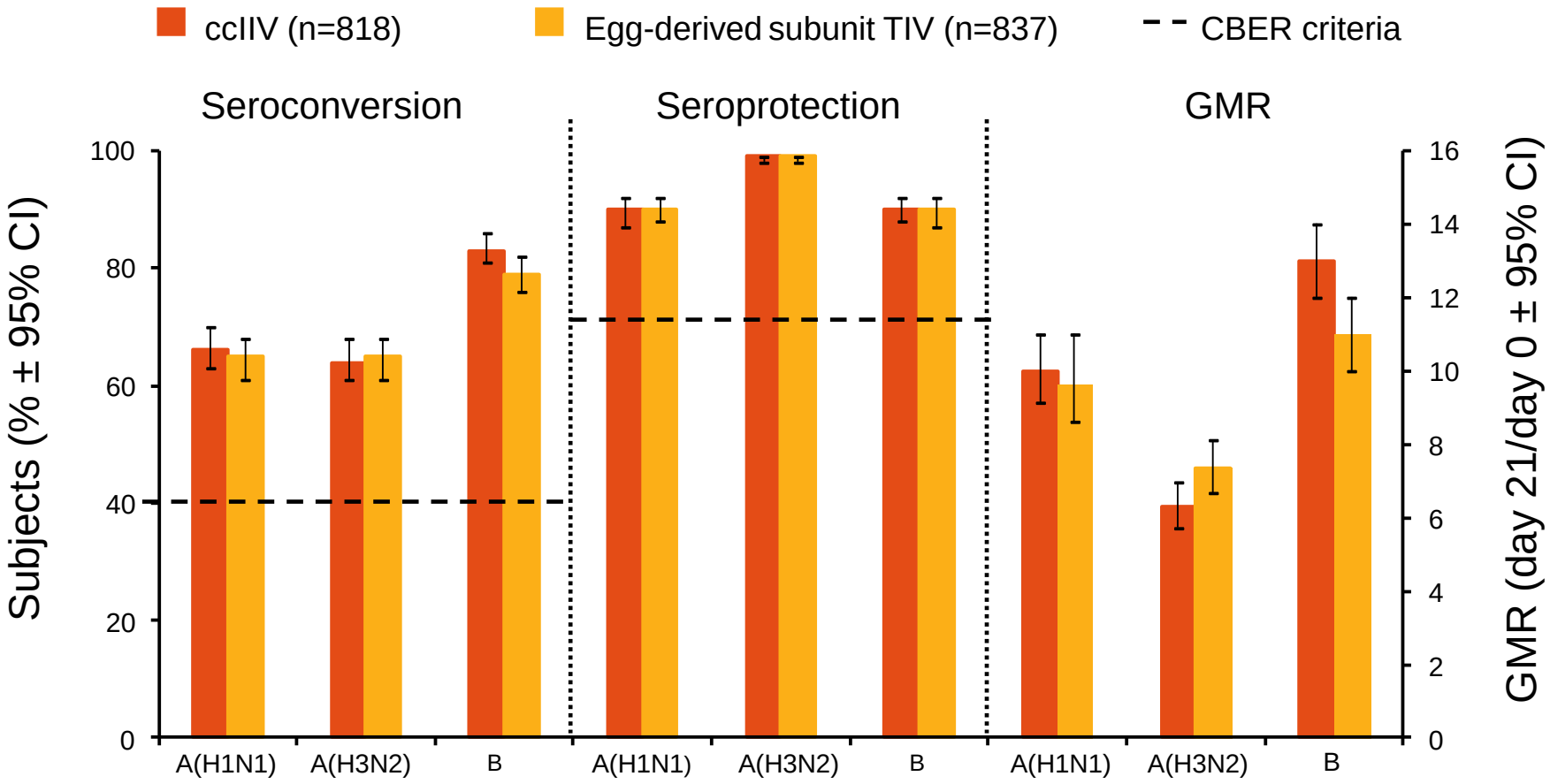
- Vaccination with ccIIV reduced the rate of community-acquired influenza compared to placebo
  - Rates of laboratory-confirmed influenza were reduced for both vaccine-like strains as well as all circulating strains

Safety and Tolerability

- ccIIV was well tolerated during the 21 day study period
  - Thirteen percent (13%) of ccIIV subjects reported an unsolicited AE. The frequency was similar in the comparator egg-derived group
  - SAEs in adults age 18-64 were 1% for ccIIV and for a licensed US comparator. In those over 65 the rate was 4% for ccIIV and the comparator. None were determined to be vaccine-related.

Immune Responses to ccIIV in Adults 18-64 Years of Age

V58P4; Phase III trial, adults (18-64 years of age), HI immune responses, Day 21 post-vaccination, 2004/05 season



GMR, geometric mean ratio ; HI, hemagglutination inhibition.
Although there is no CBER specified criterion for GMRs, these have been presented to provide further information on the immune response to the ccIIV and control vaccines.

Novartis Vaccines. Data on File.

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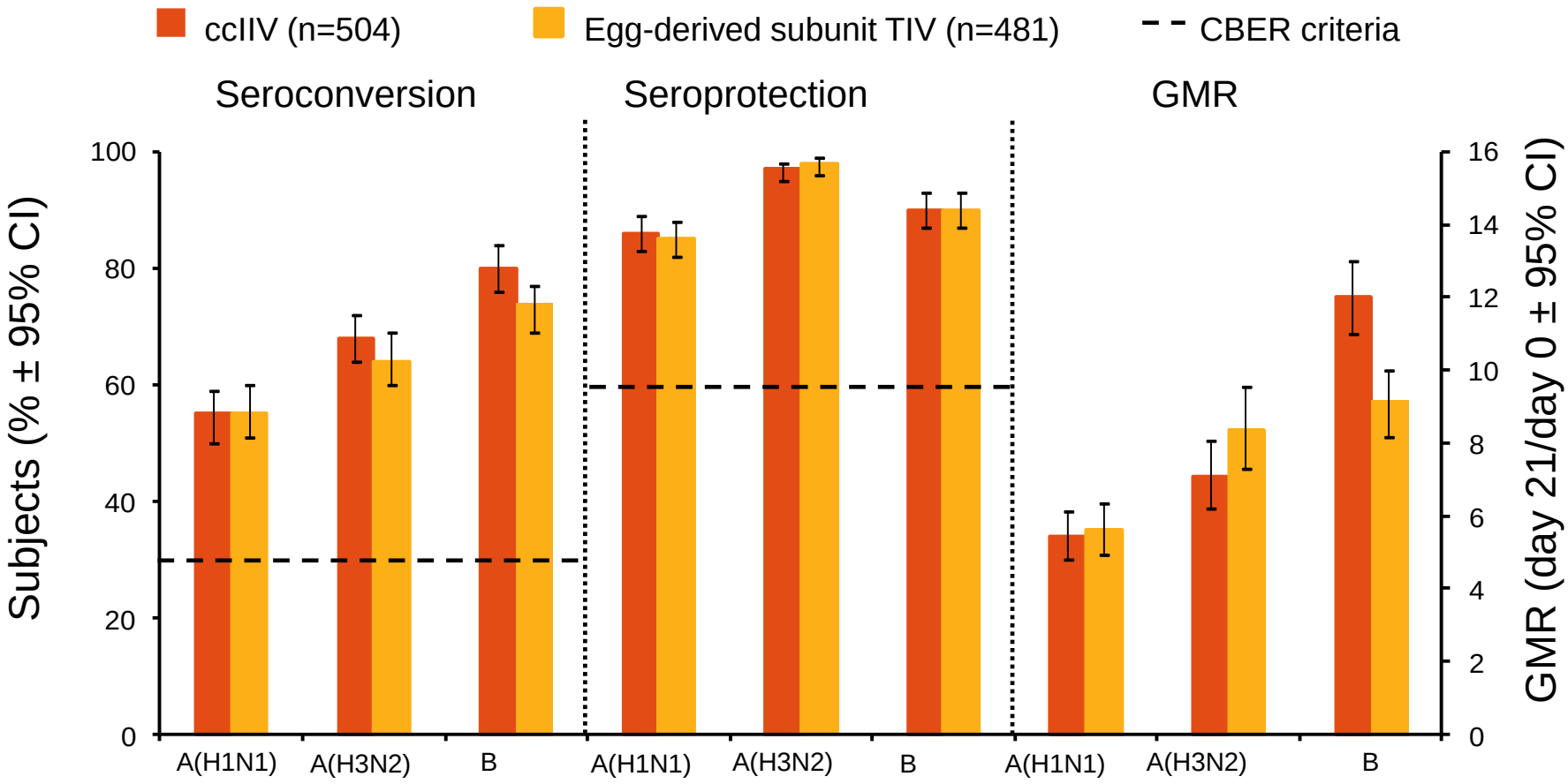
Immune Responses to ccIIV in Adults ≥ 65 Years of Age

V58P4; Phase III trial, older adults (≥65 years of age), HI immune responses, Day 21 post-vaccination, 2004/05 season



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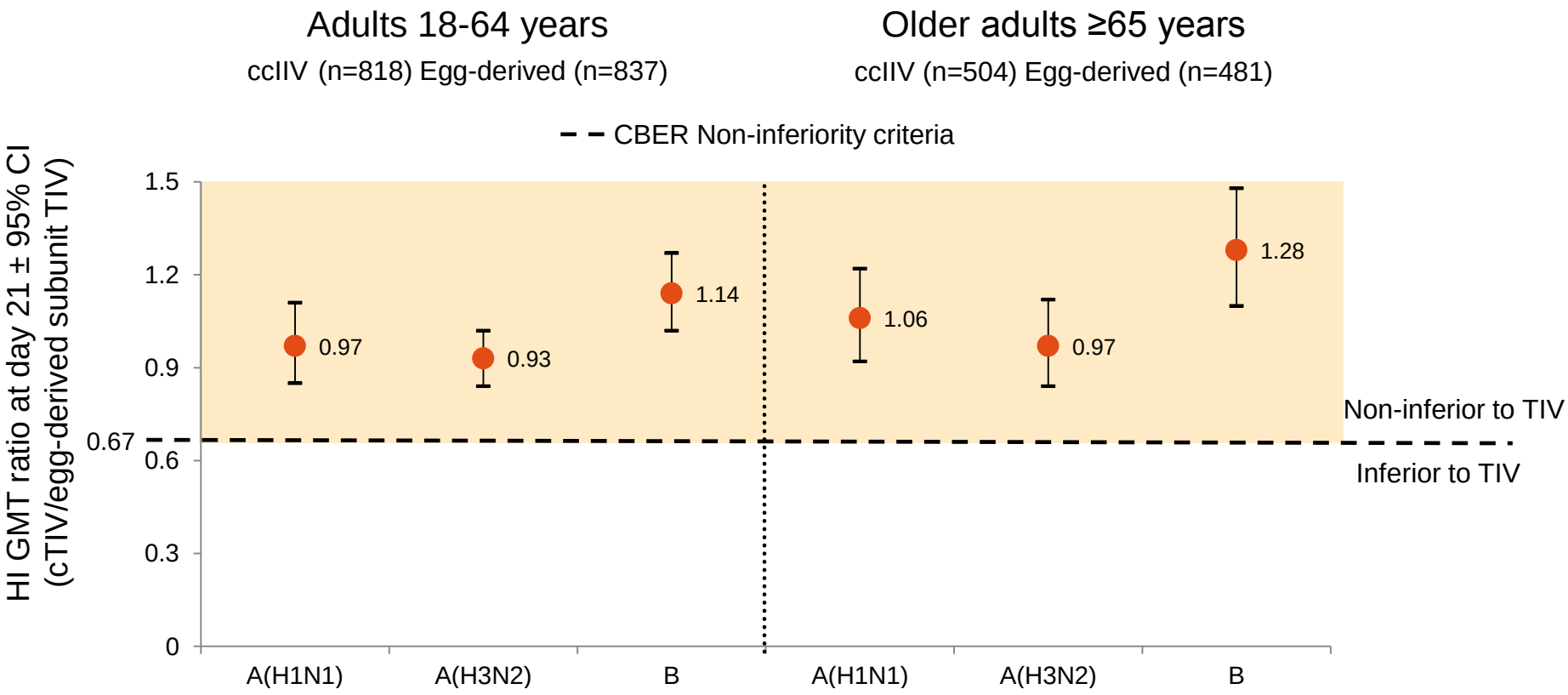
ccIIV Immune Responses Across Age Groups Were Non-Inferior to an Egg-Derived TIV

V58P4; Phase III trial, adults (≥18 years of age), non-inferiority of day 21 post-vaccination HI GMT ratios, 2004/05 season



Horizontal dashed line indicates limit for noninferiority of ccIIV vs egg-derived subunit TIV. US CBER guidance criterion for noninferiority, for each of the 3 strains, the lower limit of the 95% CI of the postvaccination GMT ratio (ccIIV/egg-derived subunit TIV) must be above 0.67.
CBER, Center for Biologics Evaluation and Research; GMT, geometric mean titer; TIV, trivalent influenza vaccine.

Novartis Vaccines. Data on File.

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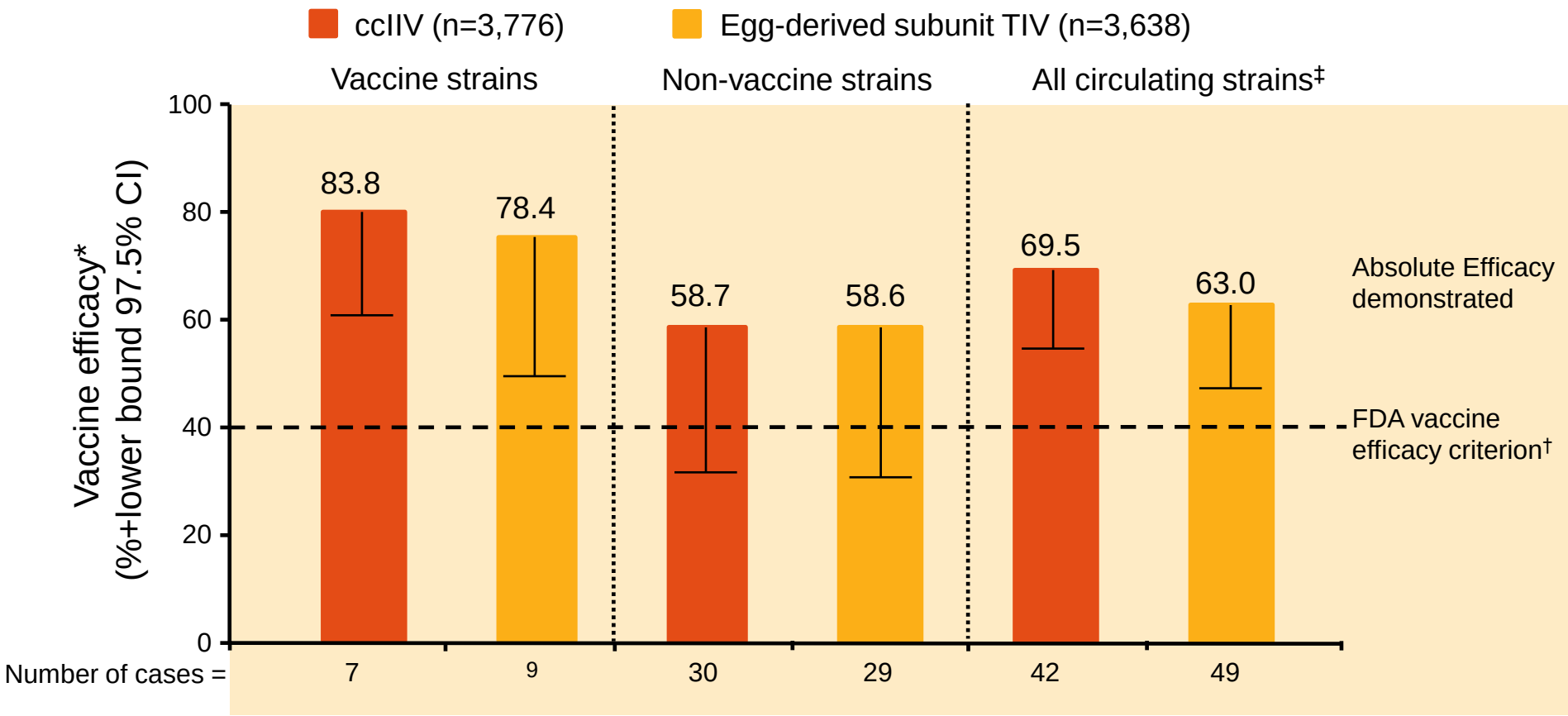
Efficacy Against Circulating Strains: ccIIV and Egg-derived TIV Compared to Placebo

V58P13; *Phase III trial, adults (18-49 years of age), vaccine efficacy against culture-confirmed influenza for vaccine-like, non-vaccine-like and all circulating strains*



*Vaccine efficacy compared to placebo. †Lower bound of two-sided 95% CI >40%. ‡ 5 influenza cases in the TIV group, 11 in the TIV group and 22 in the placebo group included because influenza confirmed by culture or PCR but the virus strain could not be characterized.

Frey S, et al. *Clin Infect Dis* 2010;51:997-1004.

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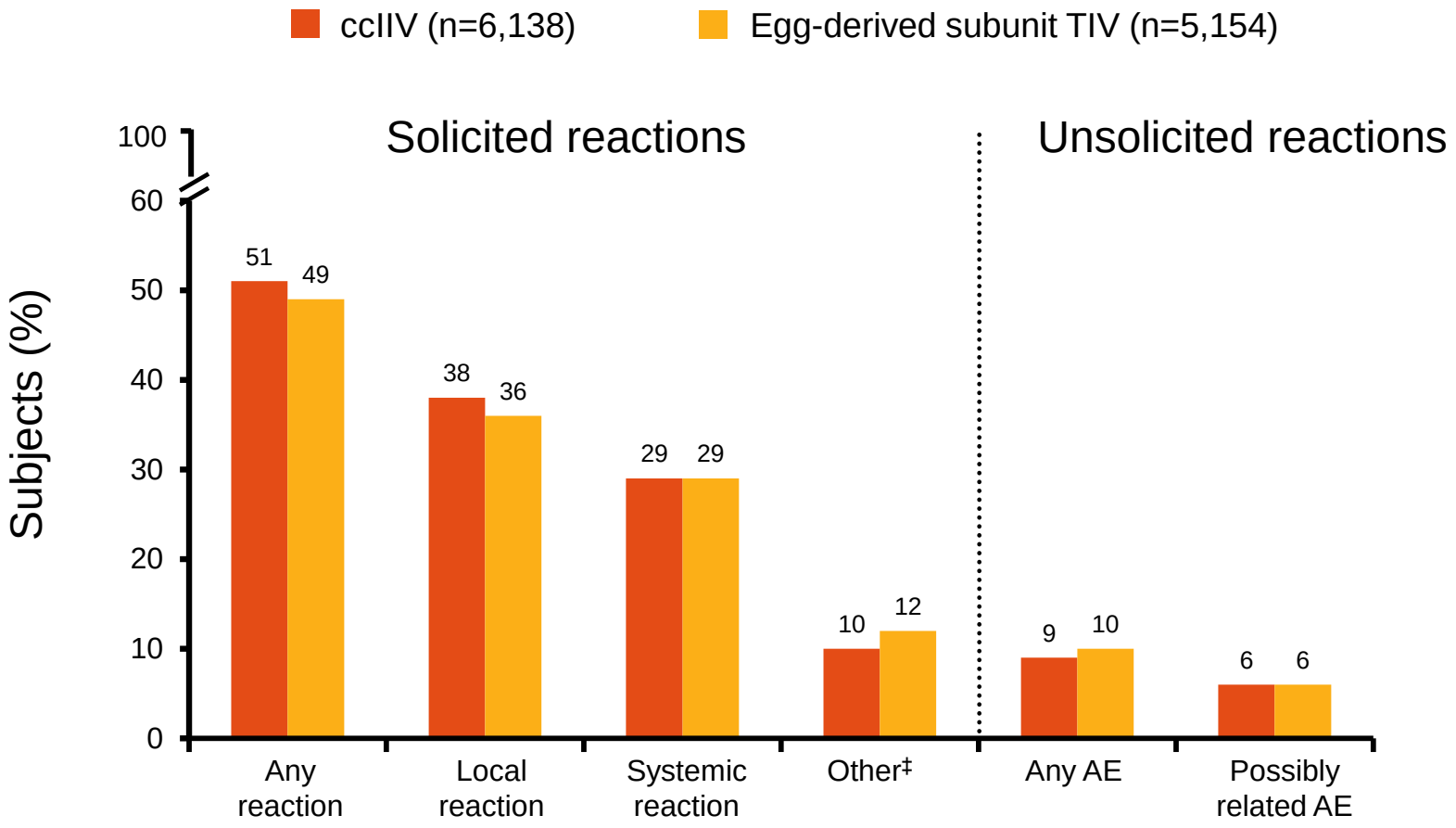
Safety and Tolerability of ccIIV in Adults 18-64 Years of Age

Pooled safety population, adults (18–64 years of age), solicited and unsolicited reactions (up to 7 days post-vaccination)*



*V58P1, V58P2, V58P4, V58P5, V58P9 and V58P13

‡ Stayed home due to a reaction and/or used analgesic or antipyretic medication

Novartis Vaccines. Data on File.

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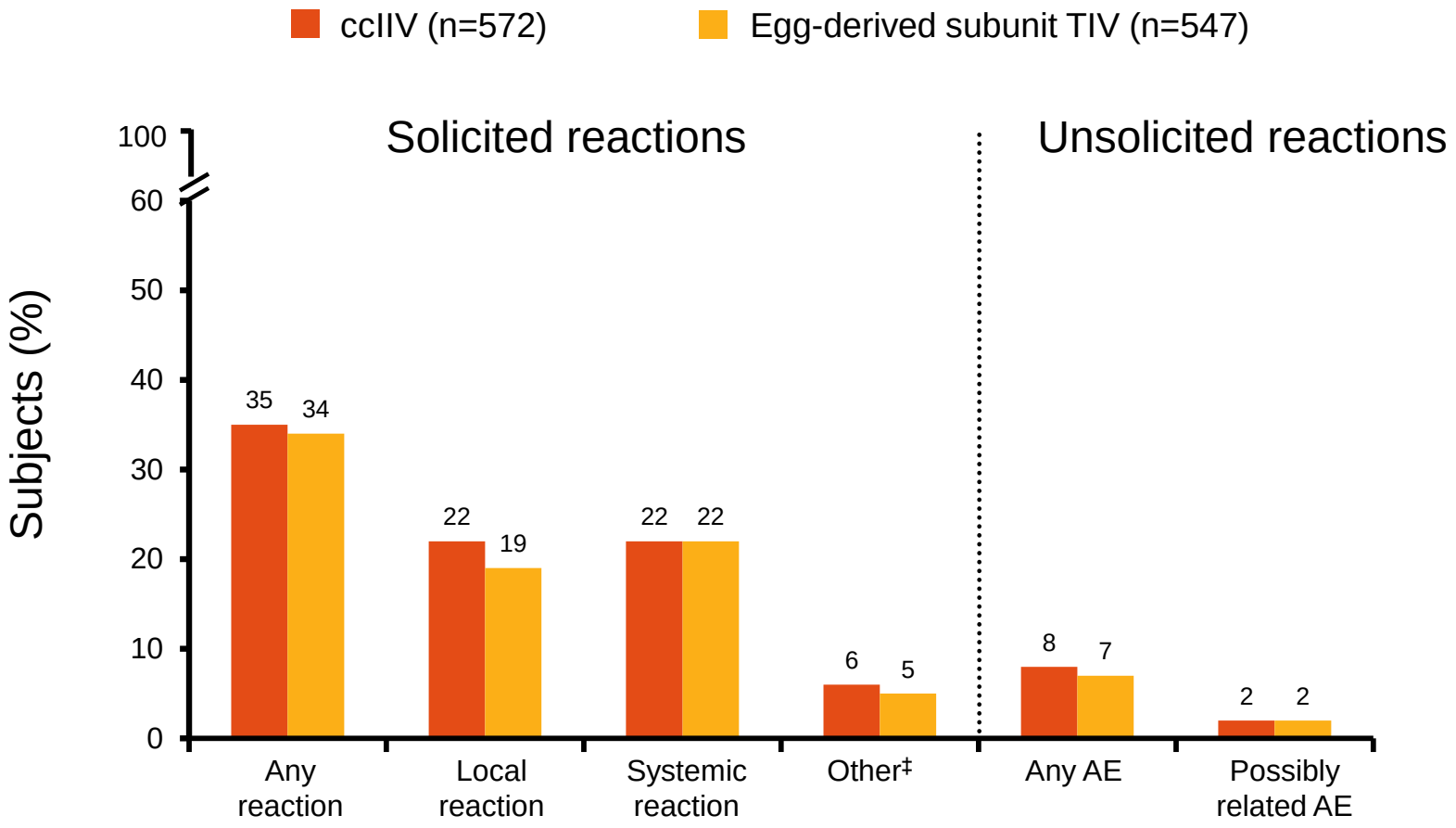
Safety and Tolerability of ccIIV in Adults ≥ 65 Years of Age

Pooled safety population, older adults (≥ 65 years of age), solicited and unsolicited reactions (up to 7 days post-vaccination)*



*V58P1, V58P2 and V58P4

‡ Stayed home due to a reaction and/or used analgesic or antipyretic medication

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Summary

- A cell-culture based influenza vaccine would offer an important manufacturing alternative to egg-based production
  - Novartis plans to produce cell-culture based influenza vaccines at state-of-the-art facility in Holly Springs, North Carolina
- Novartis cell-culture based influenza vaccine BLA is now under review for use in individuals ≥ 18 years of age
  - Submission of ≥ 3 year age planned