Better Health, Brighter Future

A Recombinant Tetravalent Dengue Vaccine Candidate Using DENV-2 Backbone

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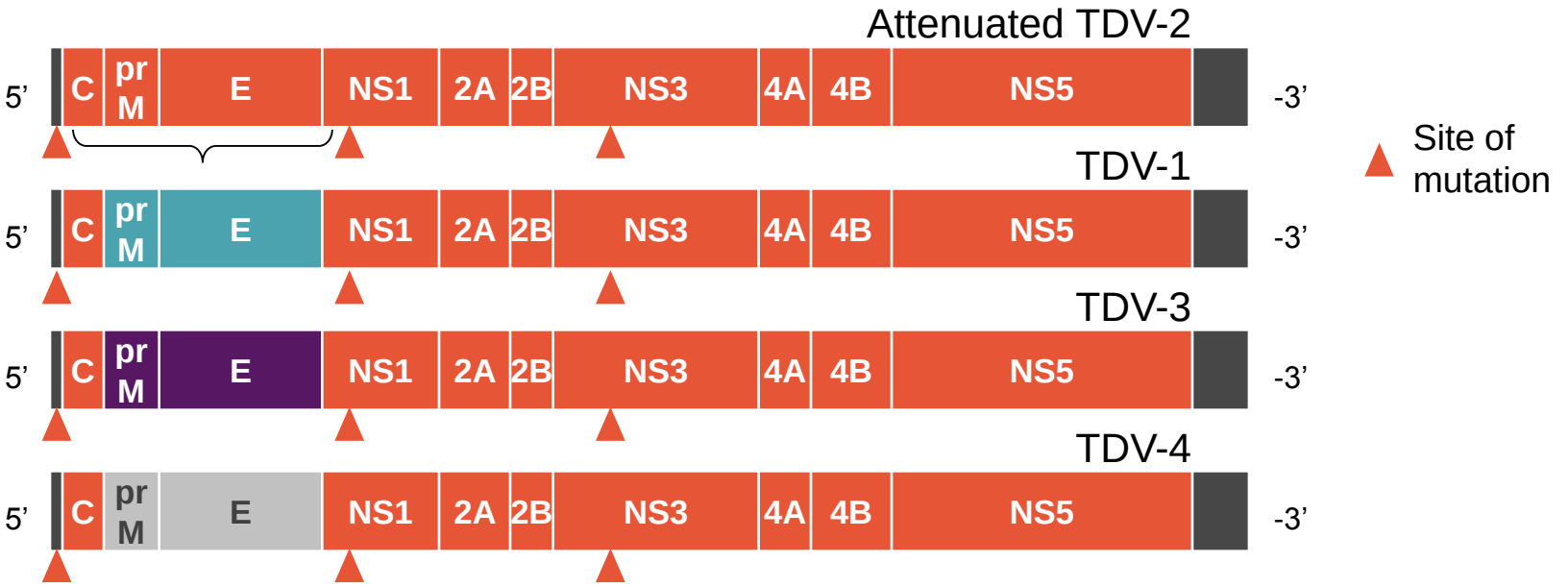
Pedro Garbes, MD.
Regional Medical Director, Latin America.
Takeda Pharmaceutical Limited

Takeda's live-attenuated tetravalent dengue vaccine (TDV) candidate is a DENV-2-based recombinant vaccine[1,2]



- Live, attenuated TDV-2 induces immune responses to DENV-2
- Recombinant TDV-1, TDV-3 and TDV-4 induce antibodies against DENV-1, DENV-3 and DENV-4 respectively
- TDV-2 backbone induces multifunctional and cross-reactive CD8+ T-cell responses to dengue non-structural proteins[3,4,5]

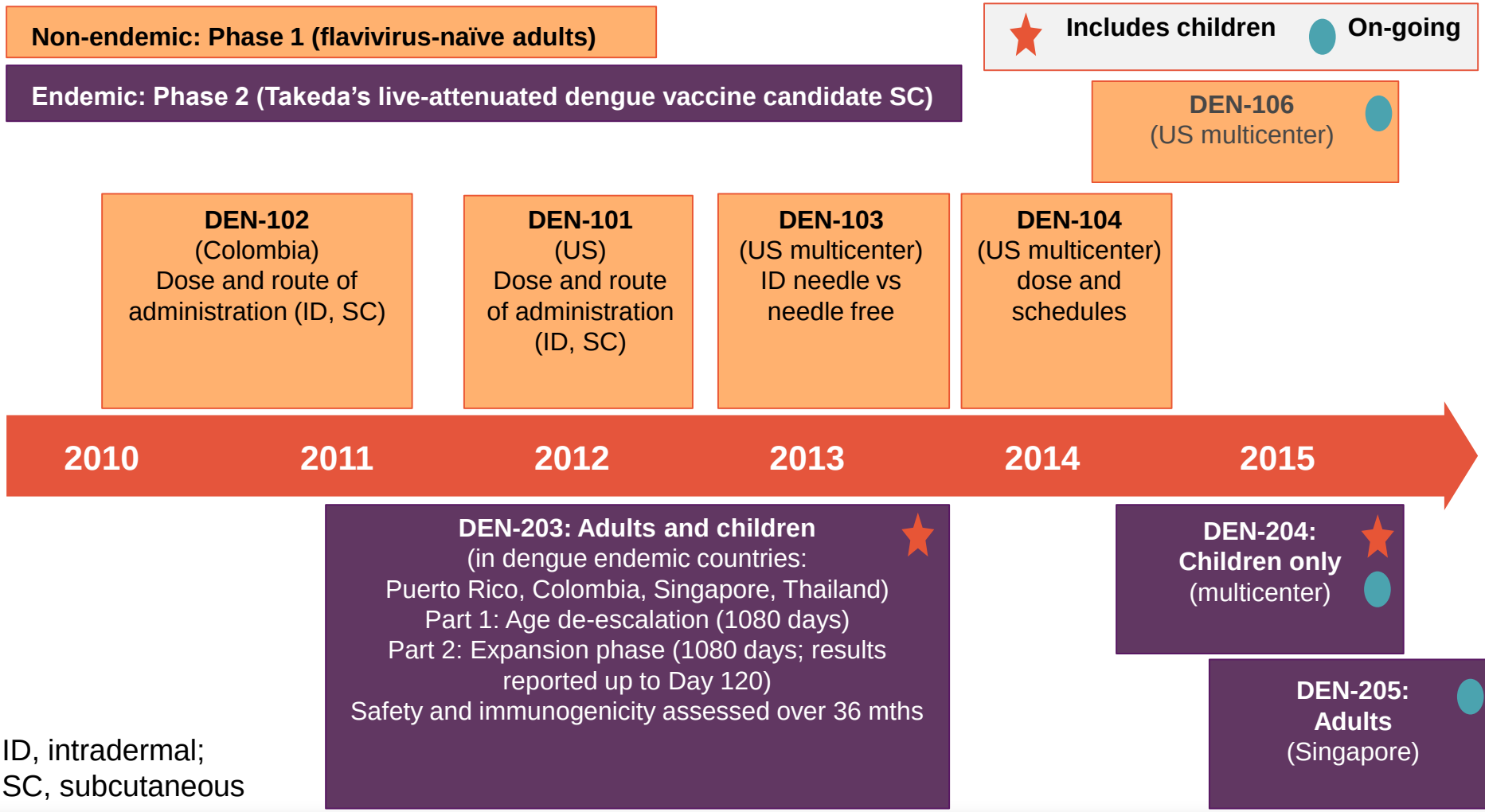
1.Osorio JE, et al. Am J Trop Med Hyg 2011;84:978:87.
2.Osorio, J. E., et al. Vaccine 2011;29(42):7251–60
3. Ambuel Y, et al. Front Immunol 2014;5:263.
4. Partidos. ASTMH 2014; Poster no. 182
5. Chu H, et al. J Infect Dis. online May 5, 2015; doi:10.1093/infdis/jiv258

Takeda's Live Attenuated Dengue Vaccine Candidate in Non Human Primates (NHP) - Protection Studies

- **Seven challenge studies completed in NHPs (more in progress) [1,2]**
  - Formulation ratios, Routes of administration (SC vs ID), Vaccination schedules
- **TDV generates immune response to 4 dengue serotypes with higher antibody titers to DENV-2**
- **TDV induces cellular immunity**
  - **Adoptive T cell transfer provides partial protection in AG129 mice[2]**
  - **Takeda's Live Attenuated Dengue Vaccine Candidate elicits CD8+ T cell responses to DENV-2 and DENV-4 envelope and non-structural proteins in non-human primates[3]**
- **Protection from viremia after challenge with DENV-4 even when DENV-4 titers are low has been observed in some experiments[1]**

[1]Osorio et al doi:10.4269/ajtmh.2011.10-0592
[2]Takeda data on file
[3]Ambuel et al doi:10.3389/fimmu.2014.00263

Phase 1 and Phase 2 studies to assess safety and tolerability of TDV and to establish dose schedule



ID, intradermal;
SC, subcutaneous

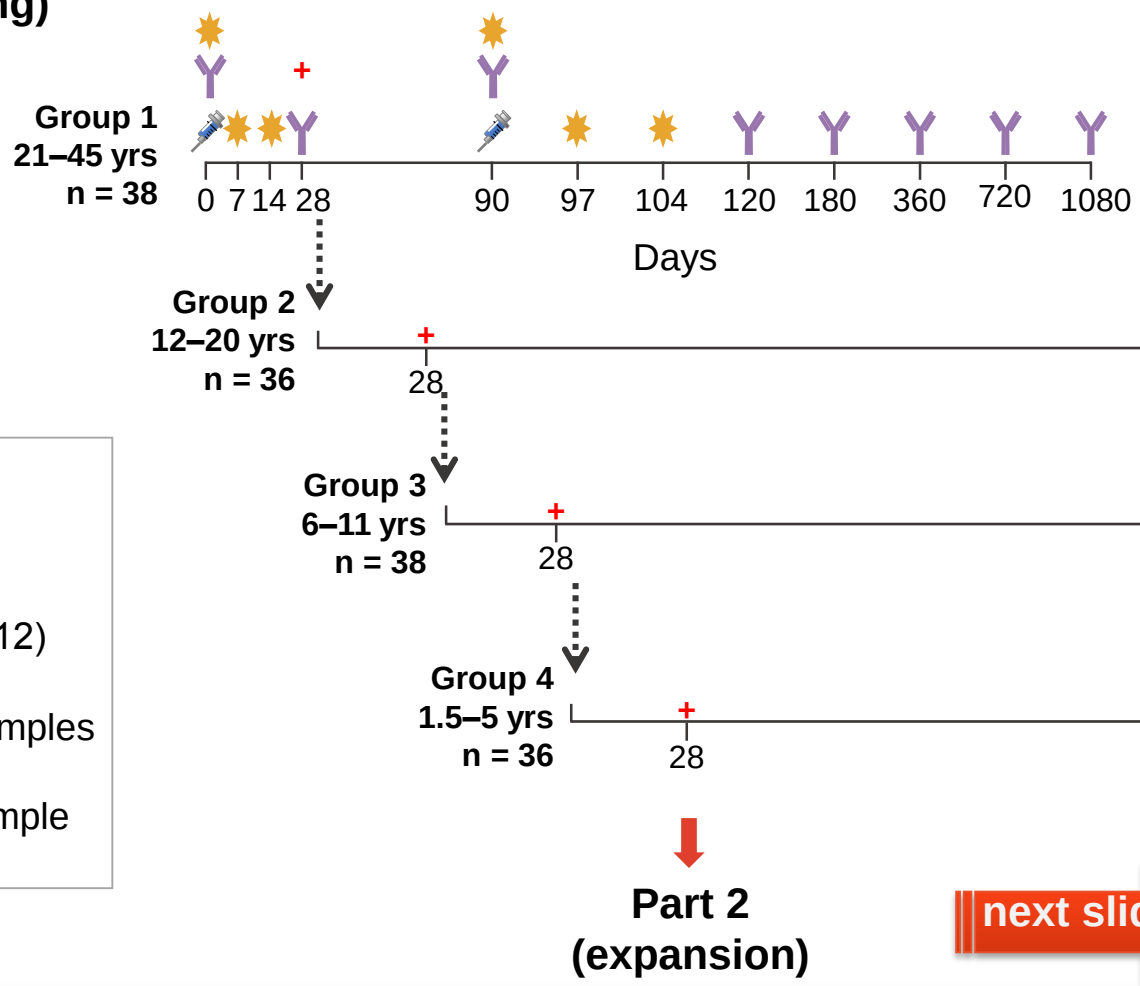
DEN-203: Randomized, Double Blind Placebo-controlled Phase 2 Trial of Takeda's

- **Primary objectives:**
  - Safety and tolerability of a subcutaneously administered recombinant tetravalent dengue vaccine in healthy adults and children (1.5 – 45 y.o.)
  - Immunogenicity of the vaccine against all four dengue serotypes
- **Clinical trial sites - dengue endemic countries**
  - Puerto Rico
    - Ponce School of Medicine – Dr. Elizabeth Barranco
    - Latin Clinical Trial Center – Dr. Carlos Sariol
    - University of Puerto Rico – Dr. Ines Esquilin
  - Colombia
    - Universidad de Antioquia - Dr. Ivan Velez
  - Singapore
    - Changi General Hospital - Dr. Helen Oh
    - National University Hospital - Dr. Lynette Shek
  - Thailand
    - Phramongkutklao (PMK) Hospital – Dr. Sriluck Simasathien
    - Faculty of Tropical Medicine, Mahidol University – Dr. Chukiat Siriwichayakul / Dr Arunee Sabchareon

DEN-203 study design: randomized, double blind, placebo-controlled Phase 2 study (Part 1)

Part 1 (age-descending)
Enrolled, n = 148

Randomization 2:1 vaccine to placebo (saline)



Key:

- Dose
- \+ Safety review (N ≥ 12)
- Viremia + safety samples
- Immunogenicity sample

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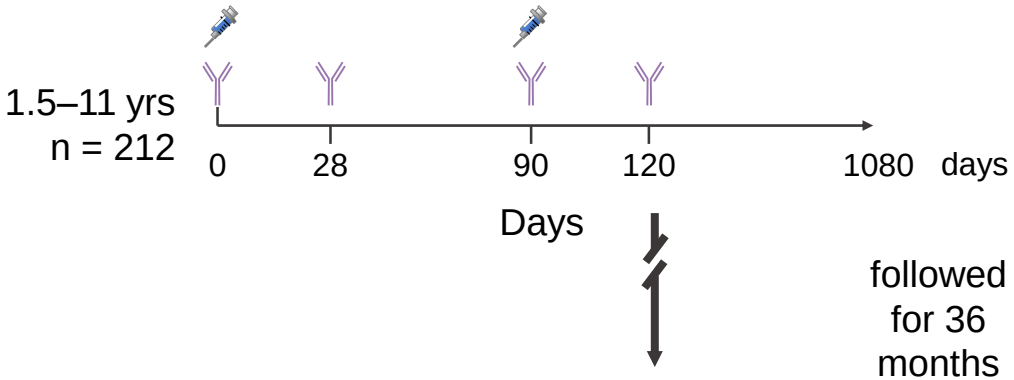
DEN-203 study Part 2: expansion in healthy children

Part 1 (age-descending) Enrolled, n = 148

Part 2 (expansion) Enrolled, n = 212

Randomization 3:1 vaccine to placebo (saline)



Key:

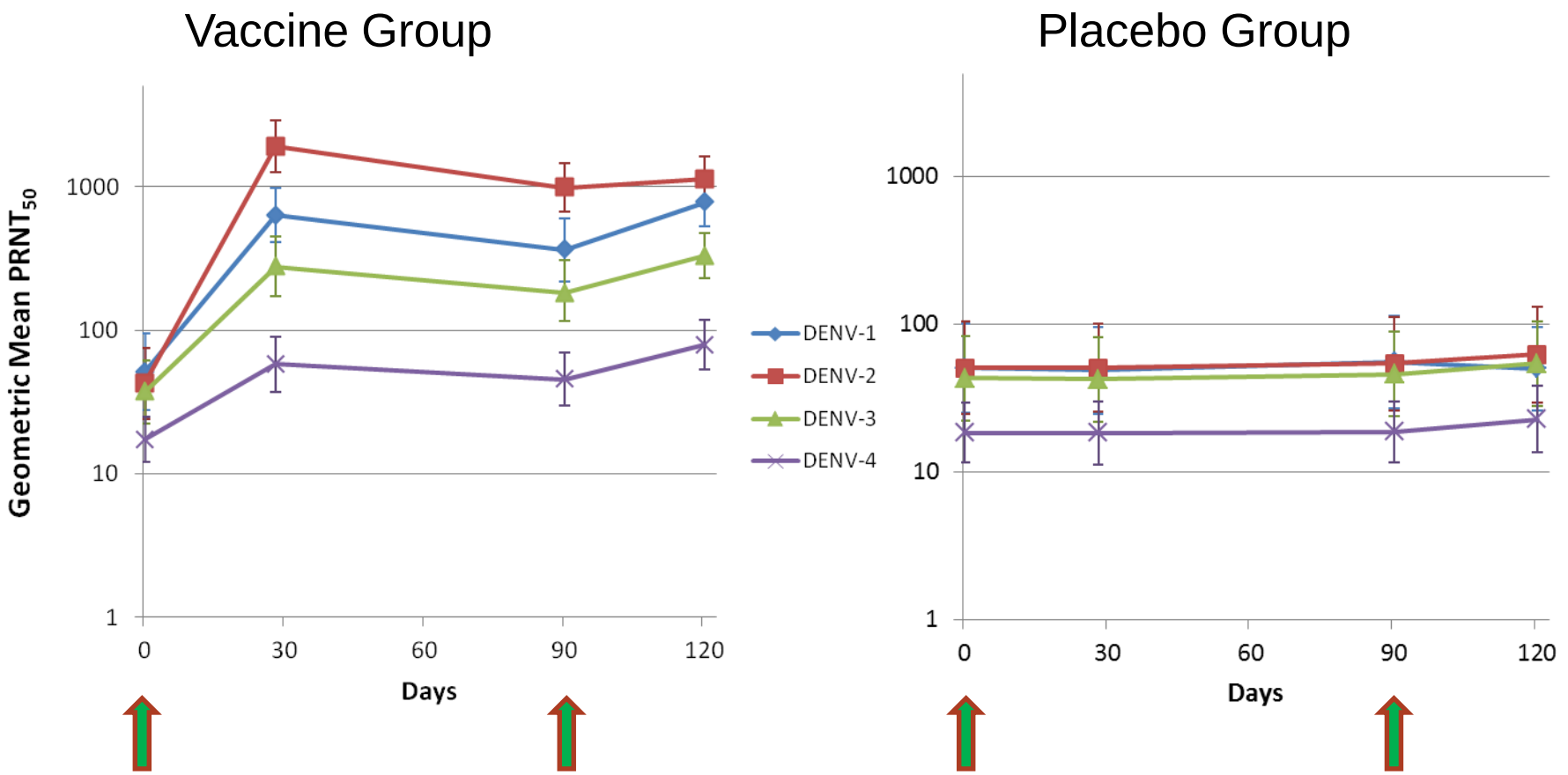
- Dose
- Immunogenicity sample

Total enrolled, n = 360

Participants administered subcutaneous placebo (PBS) or 2 vaccinations in the deltoid region:

Per dose	TDV-1	TDV-2	TDV-3	TDV-4	Total
TDV formulation (Plaque Forming Units)	2×10^4 PFU	5×10^4 PFU	1×10^5 PFU	3×10^5 PFU	4.7×10^5 PFU

DEN-203: GMTs Across Age Groups (Part 1)



Data shown as geometric means with 95% confidence intervals

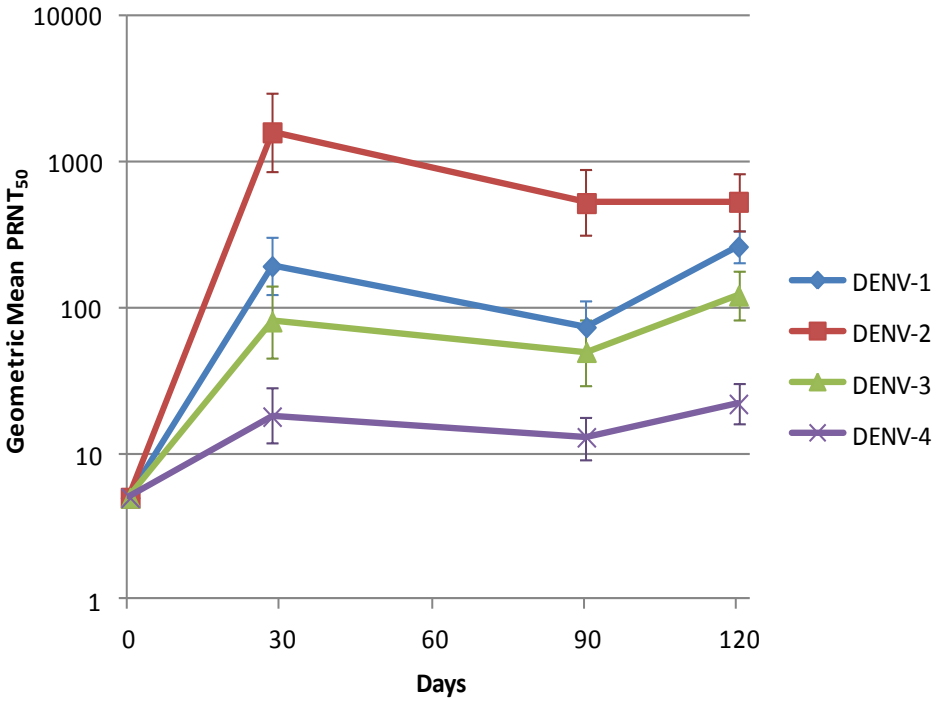
= vaccination

Sirivichayakul et al. JID 2015 (submitted)

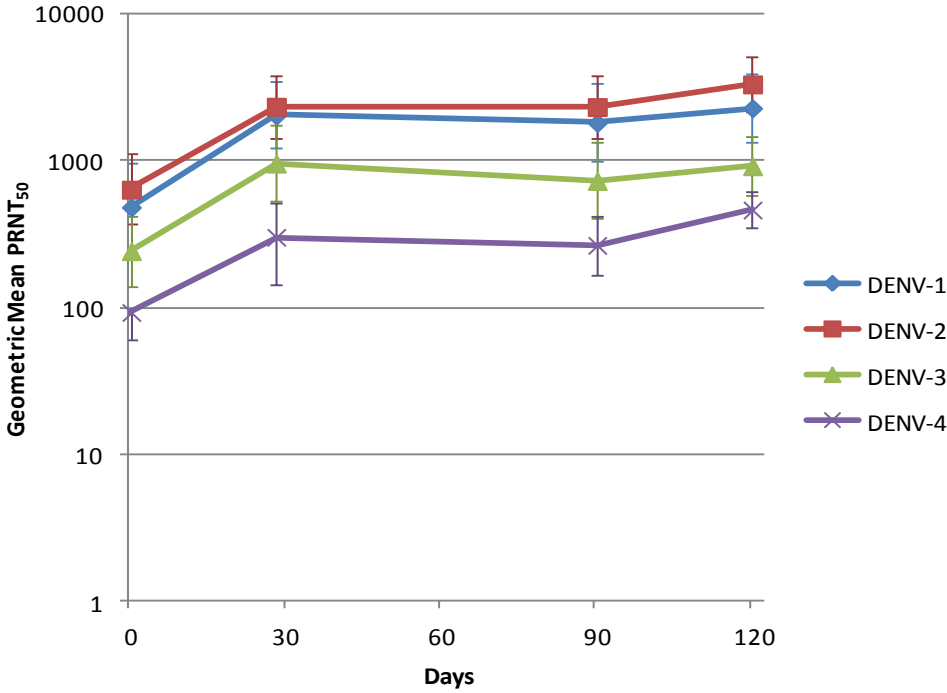
DEN-203 Immunogenicity (Part 1)

GMTs in All Age Groups by Baseline Seroresponse

Seronegative at Baseline (N=38-46)



Seropositive at Baseline (N=42-49)



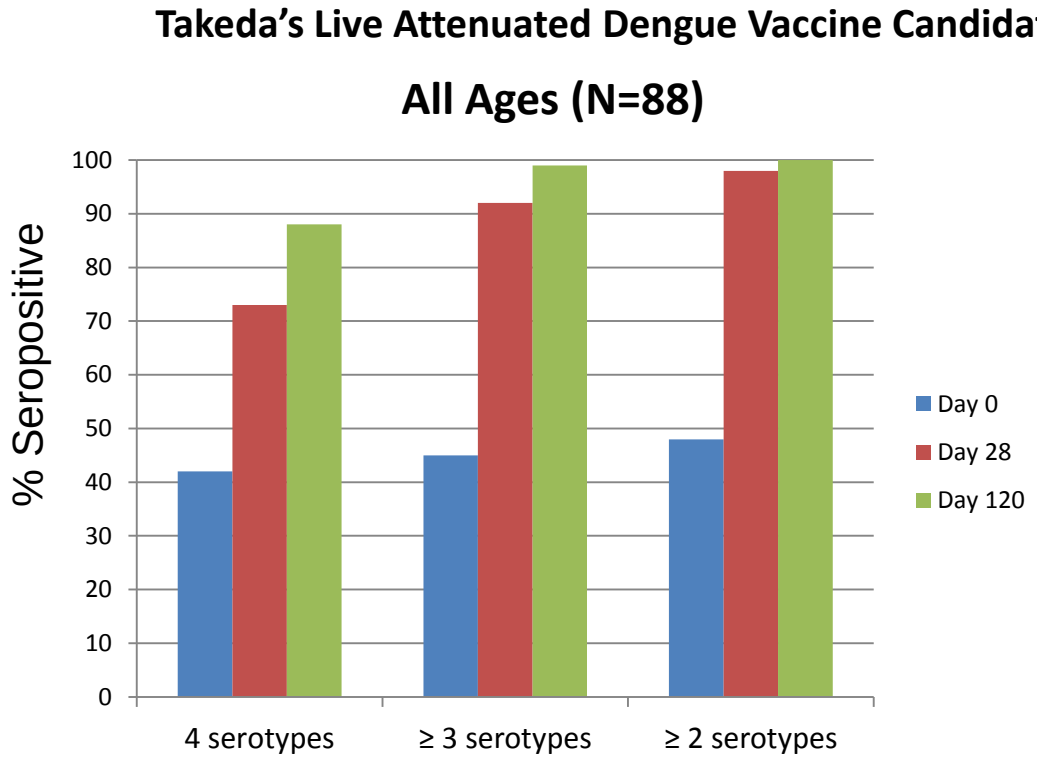
Data shown as geometric means with 95% confidence intervals

= vaccination

Sirivichayakul et al. JID 2015 (submitted)

DEN-203 Immunogenicity (Part 1)

Seropositivity Rates to Multiple Dengue Viruses – all ages



- All age groups, combined
- Doses at Day 0 and Day 90
- Seropositive = $PRNT_{50}$ titer ≥ 10

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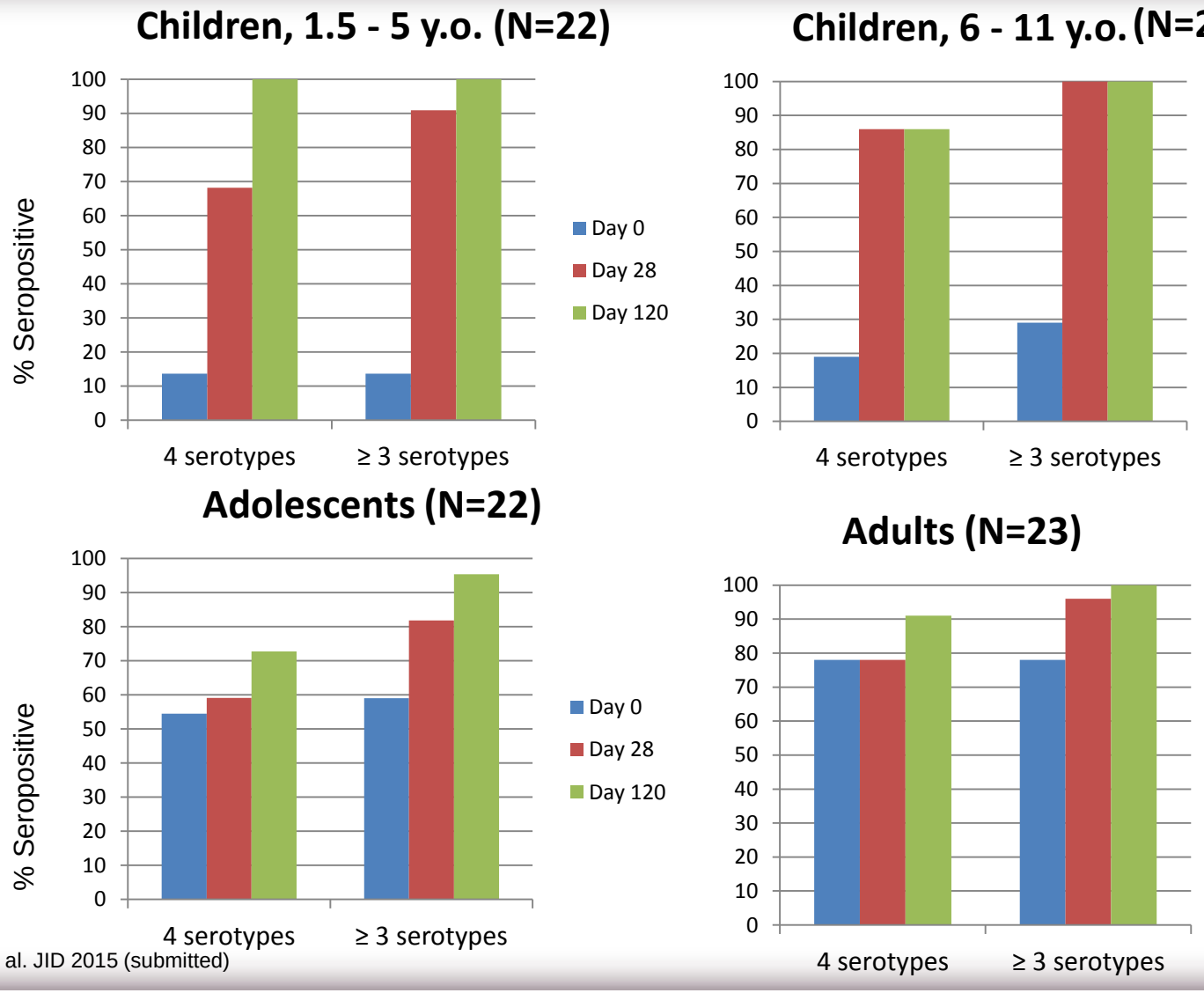
DEN-203 Immunogenicity (Part 1)

Seropositivity Rates to Multiple Dengue Viruses – age stratified



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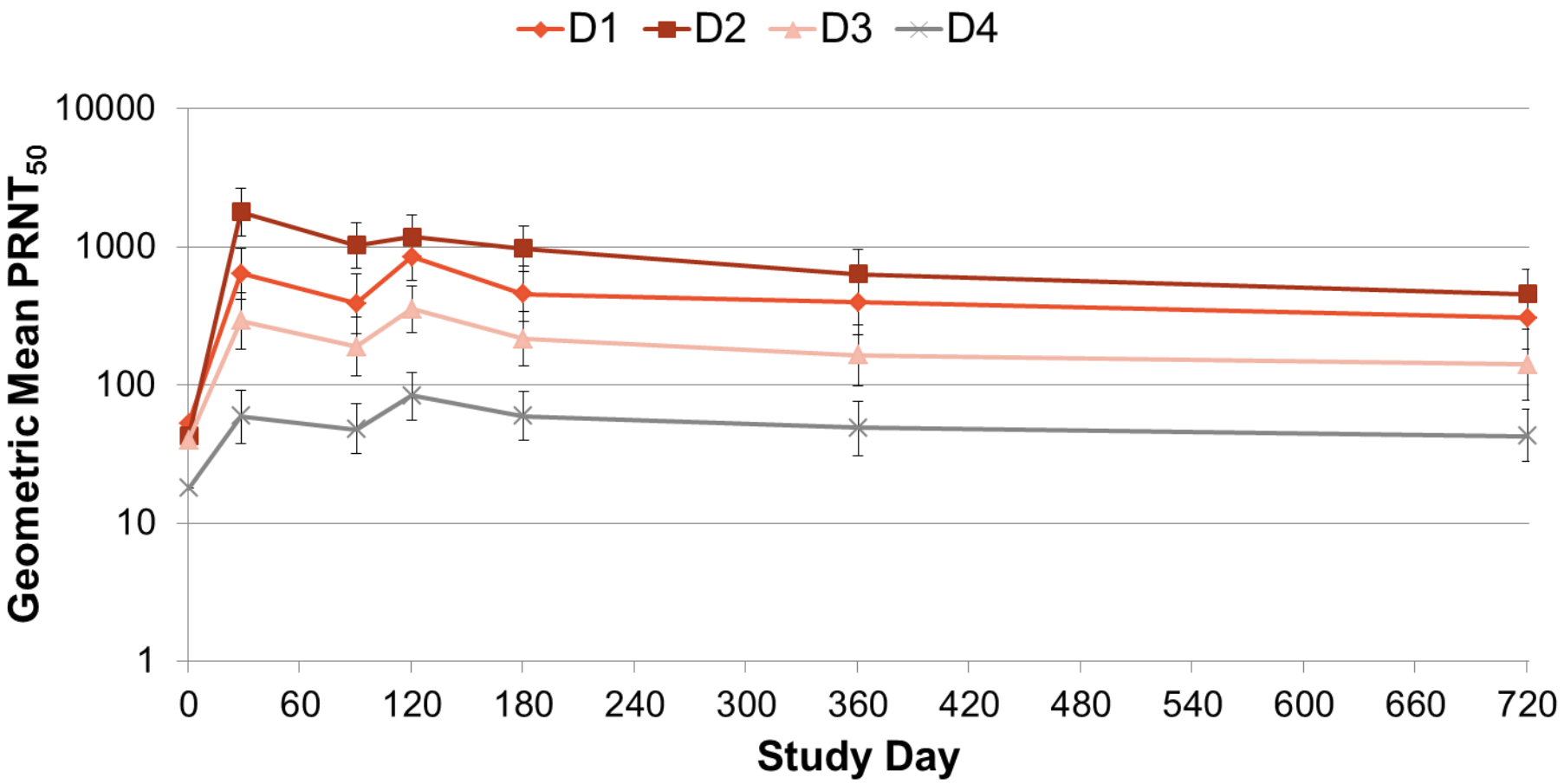
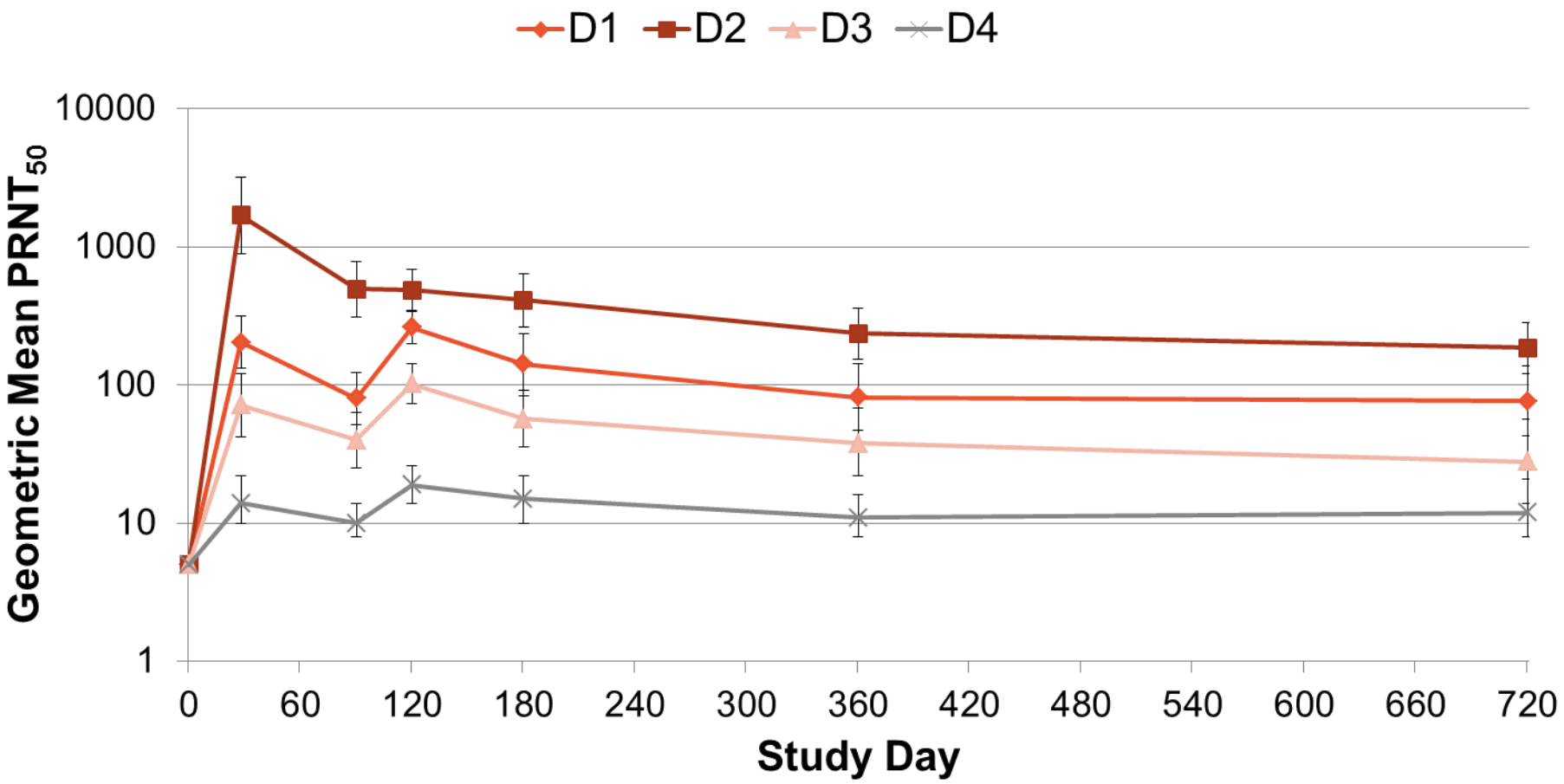
DEN 203; GMTs over time
All subjects

Combined Age Groups (N=90)



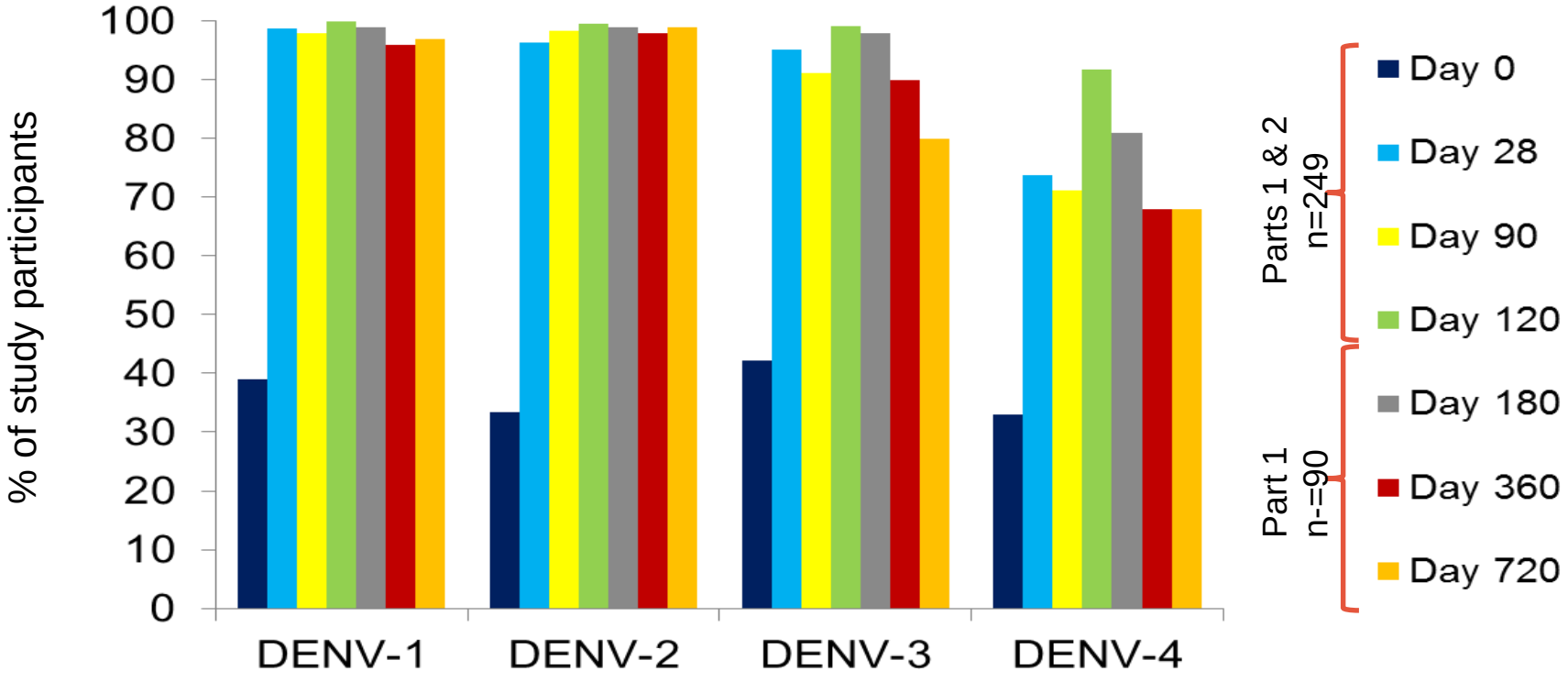
DEN 203; GMTs over time
Subjects Seronegative at baseline

Combined Age Groups (N=40)



TDV elicits high rates of seropositivity to DENV-1–4 through Day 720

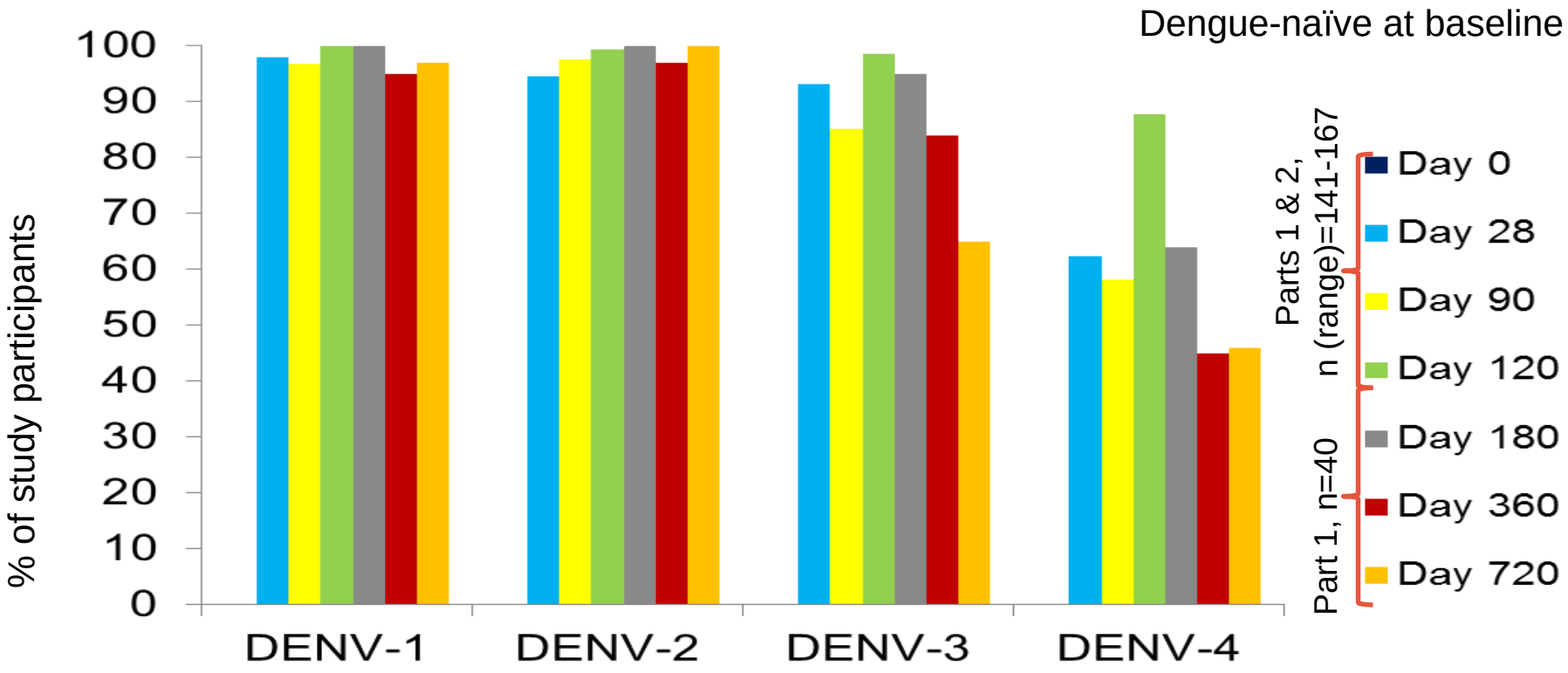
Percentage of seropositive‡ children and adults – all subjects



*full analysis set, ‡seropositive = MNT_{50} titer ≥ 10. Sirivichayakul et al. JID 2015 (submitted)

TDV elicits high rates of seropositivity to DENV-1−4, in participants who were seronegative at baseline

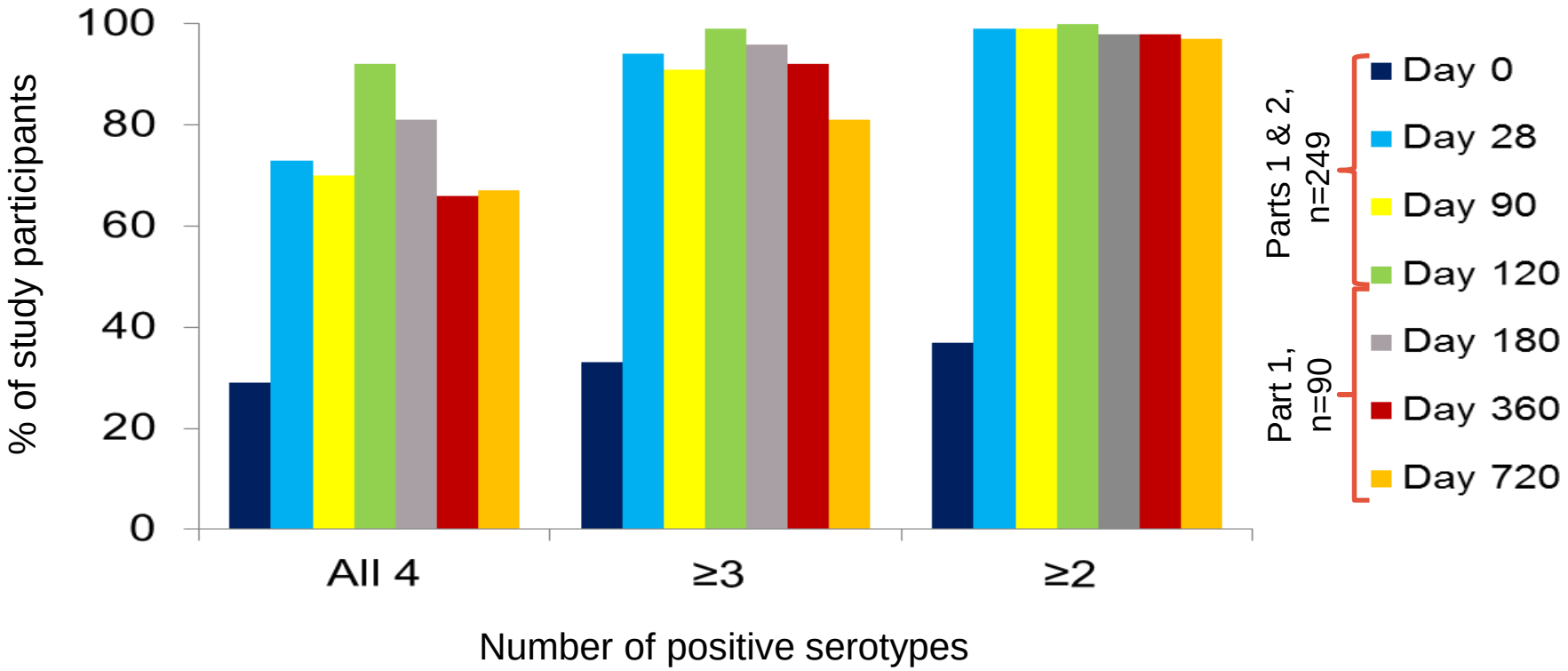
Percentage of children and adults who were seronegative at baseline and became seropositive‡ after receiving TDV



*full analysis set, ‡seropositive = MNT_{50} titer ≥ 10. Sirivichayakul et al. JID 2015 (submitted)

TDV elicits a tetravalent response in the majority of children and adults

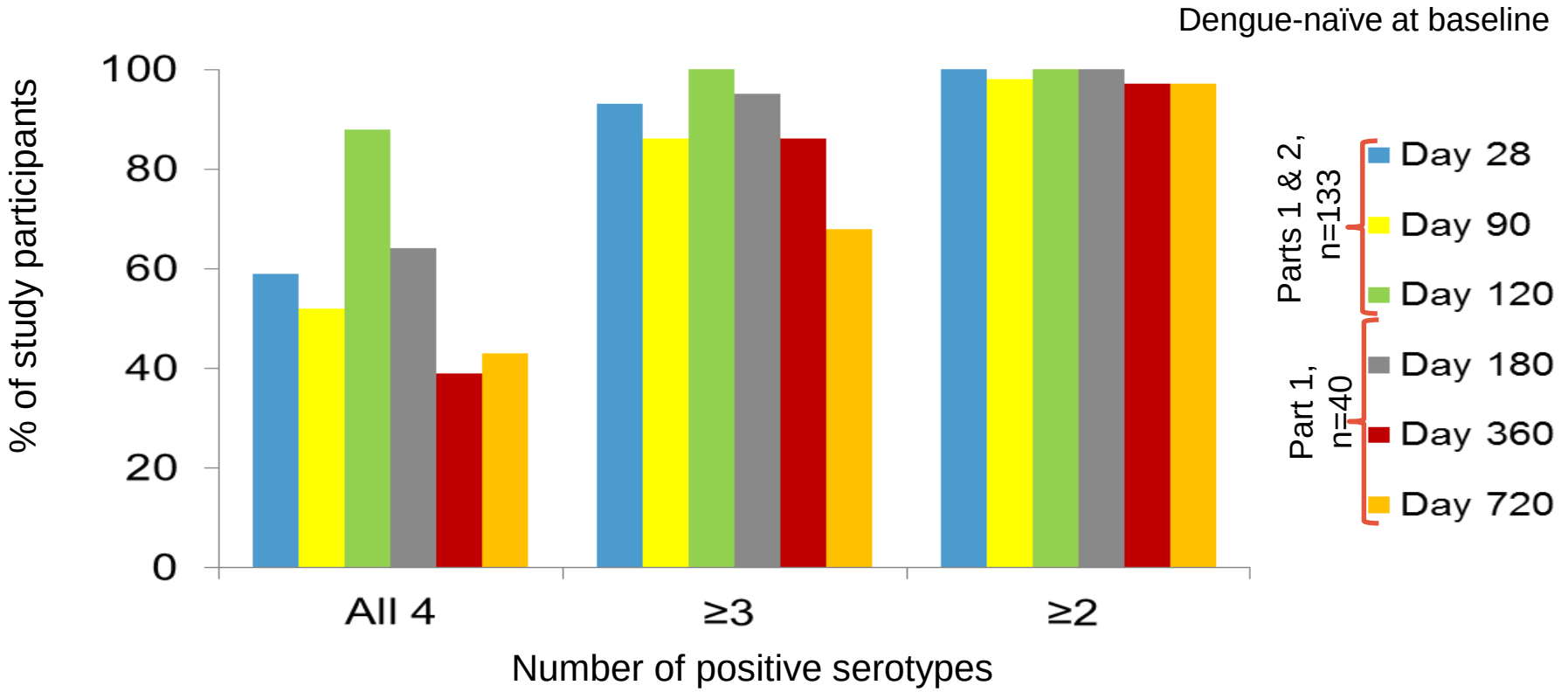
Percentage of children and adults seropositive‡ to multiple serotypes



***full analysis set: includes all participants regardless of baseline seropositivity**, Sirivichayakul et al. JID 2015 (submitted)
‡seropositive = MNT_{50} titer ≥ 10

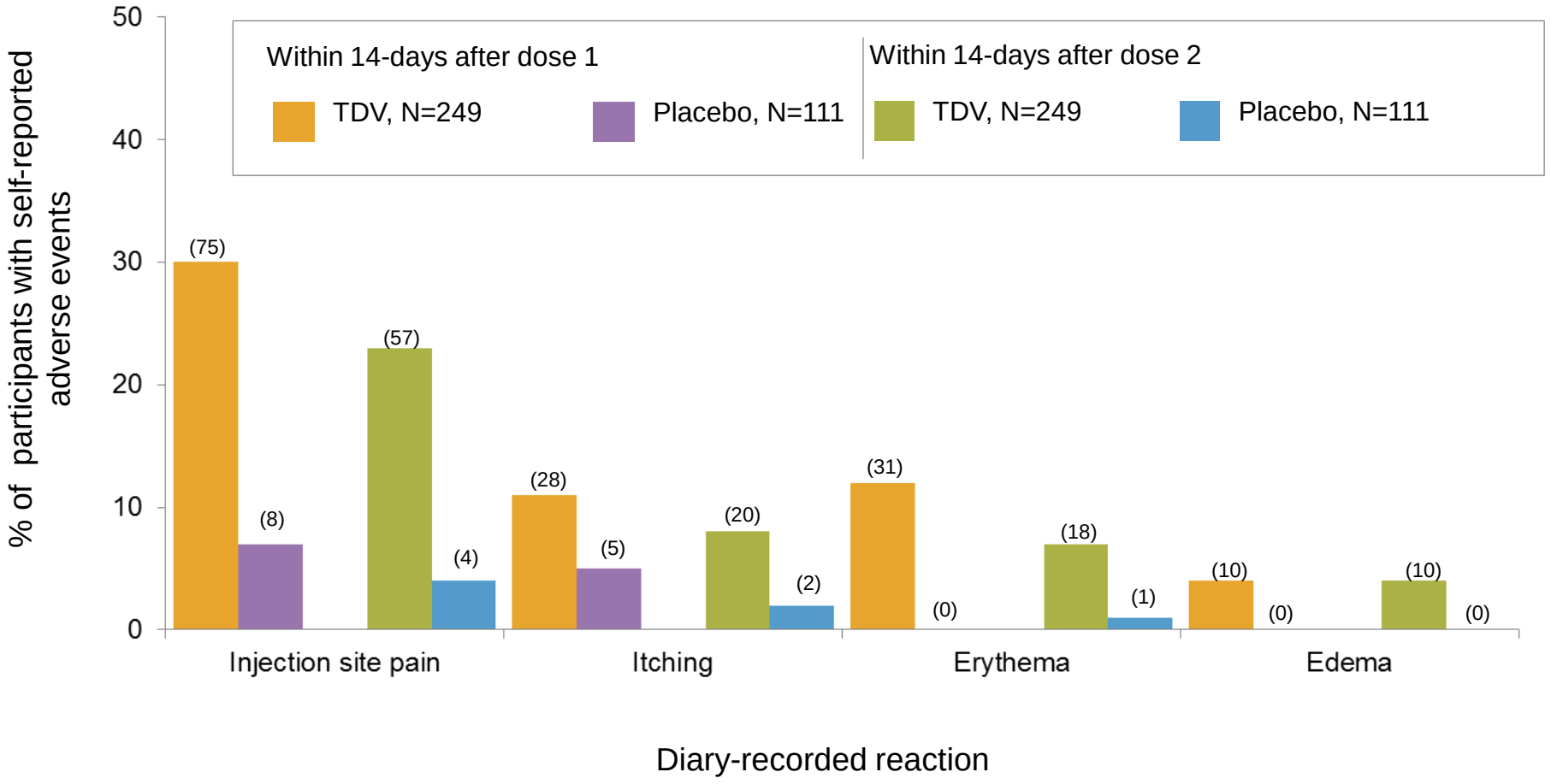
TDV elicits a tetravalent response in children and adults, in participants who were seronegative at baseline

Percentage of children and adults who were seronegative at baseline and became seropositive‡ to multiple serotypes after receiving TDV



* Sirivichayakul et al. JID 2015 (submitted)
‡seropositive = MNT_{50} titer ≥ 10

The incidence of injection site AEs, but not systemic AEs was greater after TDV administration compared to placebo



Safety set, Sirivichayakul et al. JID 2015 (submitted)

DEN- 203 Safety Summary

- **No discontinuations due to AEs**
- **No related SAEs**
- **No constellation of symptoms suggestive of dengue fever**
- **No serious vaccine-related adverse events (SAEs) assessed, as related by investigators**
- **No meaningful changes in blood chemistry, hematology**
- **Most common AEs**
  - Self limited mild to moderate systemic adverse events:
    - Headache, nasopharyngitis, nausea and myalgia were most common
    - All grade 3 and 4 AEs not related to the vaccine
    - No constellation of symptoms suggestive of dengue fever
  - Short-duration (<4 days) mild-to-moderate local injection site reactions (erythema, edema and pain)
- **No deaths**

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Current Status: Subjects Enrolled in TDV Studies

	TDV	Control	Total
Completed Studies			
DEN 101	48	24	72
DEN 102	79	17	96
DEN 103	67	0	67
DEN 104	136	0	136
DEN 203	249	111	360
Ongoing Studies			
DEN 106	1002	0	1002
DEN 204	1600	200	1800
Total	3181	352	3533

As of Aug/2015

Takeda's Live Attenuated Dengue Vaccine Candidate: Clinical Summary

- All dose formulations of Takeda's Live Attenuated Dengue Vaccine Candidate tested in phase I and II studies were well tolerated.
- In a phase II study, Takeda Candidate Vaccine formulation induced neutralizing antibodies and levels of seroconversion ≥80% to all four dengue serotypes after two doses.
- A formulation with an optimized component ratio has been selected for ongoing and future studies.
- A pivotal phase III efficacy study is in preparation.

Acknowledgements

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US: Sarah George

Phase 2 Sites:

Puerto Rico: C. Sariol, I. Esquilin, E. Barranco
Colombia; I. Velez
Singapore: H. Oh, L. Shek
Thailand: A.Sabchareon, S. Simasathien, C. Sirivichayakul

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Thank you

Takeda Pharmaceutical Limited