



Takeda's Tetravalent Dengue Vaccine (TDV) Candidate: An update

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- Takeda's TDV candidate
- Summary of development through phase II
- DEN-204 phase 2 endemic pediatric study-interim analysis (6 months safety and 1 month immunogenicity)
- Current status of safety database

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



- TDV-2 induces immune responses to DENV-2
- 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, *et al. Am J Trop Med Hyg* 2011;84:978:87 | 2. Osorio, *et al. Vaccine* 2011;29(42):7251–60 | 3. Ambuel, *et al. Front Immunol* 2014;5:263 | 4. Partidos. *ASTMH* 2014; Poster no. 182 | Chu, *et al. J Infect Dis.* 2015;212(10):1618-28

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



**Non-endemic: Phase 1 and 2
(flavivirus-naïve adults)**

★ Includes children

● Ongoing

**Endemic:
Phase 2**

DEN-106
(US multicenter)

DEN-102
(Colombia)
Dose and route of administration
(ID, SC)

DEN-101
(US)
Dose and route of administration
(ID, SC)

DEN-103
(US multicenter)
ID needle vs needle free

DEN-104
(US multicenter)
dose and schedules

2010

2011

2012

2013

2014

2015

DEN-203: Adults and children
(multicenter) ★ ●
Part 1: Age de-escalation
Part 2: Expansion phase

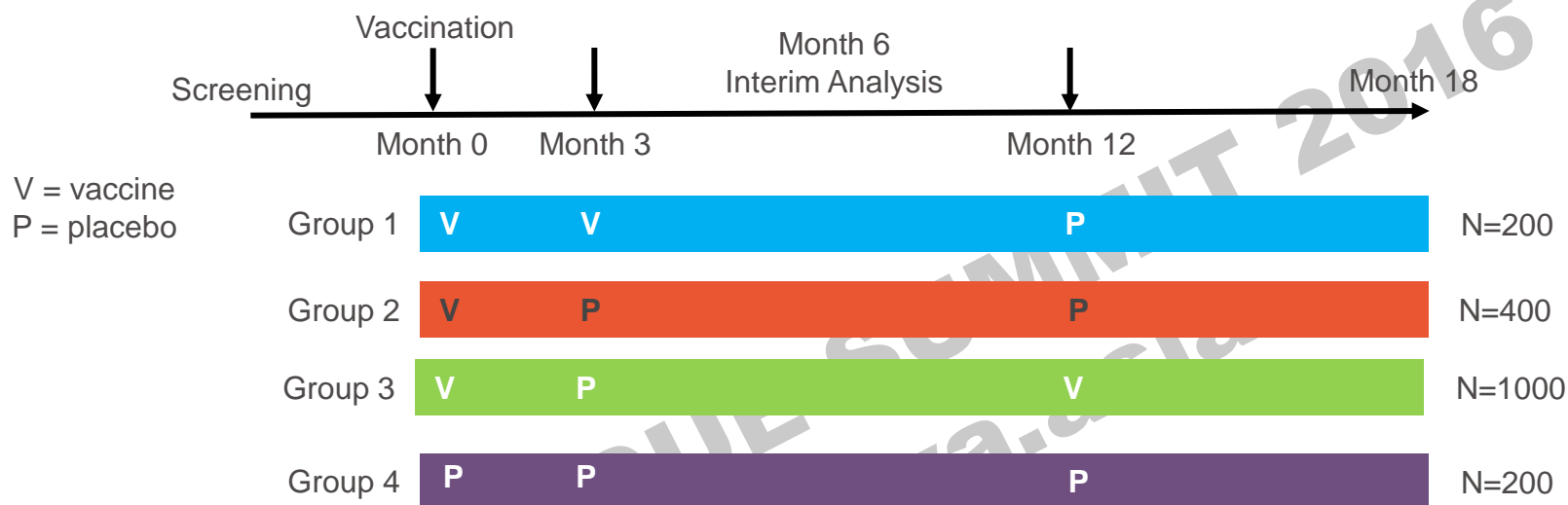
DEN-204: Children only ★ ●
(multicenter)

DEN-205: Adults ●
(Singapore)

ID, intradermal;
SC, subcutaneous

DEN-204 – Phase 2 Endemic Pediatric Study

Enrolment completed January 2015



- **Population:** Children aged 2 to <18 years in Asia and Latin America
- Descriptive comparison of two dose and one dose schedules + assessment of booster at 12 months
- A large safety database in endemic pediatric population in preparation for phase III trial

Demographics – randomized set



| | Group 1 (N=200) | Group 2 (N=398) | Group 3 (N=998) | Group 4 (N=198) | Total (N=1794) |
|--|----------------------------|----------------------------|----------------------------|----------------------------|---------------------------|
| Mean Age (SD) | 7.3 (4.01) | 7.3 (4.14) | 7.3 (4.06) | 7.0 (3.97) | 7.3 (4.06) |
| Age Groups, N (%) | | | | | |
| <i>2-5 years</i> | 85 (42.3) | 165 (41.5) | 418 (41.9) | 84 (42.4) | 752 (41.9) |
| <i>6-11 years</i> | 78 (38.8) | 158 (39.7) | 392 (39.3) | 78 (39.4) | 706 (39.3) |
| <i>12-<18 years</i> | 38 (18.9) | 75 (18.8) | 187 (18.7) | 36 (18.2) | 336 (18.7) |
| Gender, N (%) | | | | | |
| <i>Male</i> | 100 (49.8) | 191 (48.0) | 512 (51.3) | 103 (52.0) | 906 (50.5) |
| <i>Female</i> | 101 (50.2) | 207 (52.0) | 485 (48.6) | 95 (48.0) | 888 (49.5) |
| Hispanic or Latino, N (%) | 166 (82.6) | 317 (79.6) | 825 (82.7) | 158 (79.8) | 1466 (81.7) |
| Race, N (%) | | | | | |
| <i>American Indian/ Alaskan Native</i> | 102 (50.7) | 204 (51.3) | 505 (50.6) | 101 (51.0) | 912 (50.8) |
| <i>Asian</i> | 35 (17.4) | 82 (20.6) | 174 (17.4) | 40 (20.2) | 331 (18.4) |
| <i>Black/African American</i> | 64 (31.8) | 109 (27.4) | 311 (31.2) | 56 (28.3) | 540 (30.1) |
| <i>White</i> | 0 | 2 (0.5) | 8 (0.8) | 1 (0.5) | 11 (0.6) |

Baseline Seropositivity status – immunogenicity subset



| | Group 1 (N=91) | Group 2 (N=187) | Group 3 (N=191) | Group 4 (N=93) | Total (N=562) |
|---------------------------------|-------------------------------|--------------------|--------------------|-------------------|-------------------|
| | Number (%) of Subjects | | | | |
| N evaluated | 87 | 181 | 183 | 90 | 541 |
| 2-5 years | 28 | 57 | 63 | 32 | 180 |
| 6-11 years | 36 | 78 | 72 | 38 | 224 |
| 12-<18 years | 23 | 46 | 48 | 20 | 137 |
| Positive (any serotype) | 45 (51.7) | 105 (58.0) | 100 (54.6) | 47 (52.2) | 297 (54.9) |
| 2-5 years | 11 (39.3) | 28 (49.1) | 31 (49.2) | 13 (40.6) | 83 (46.1) |
| 6-11 years | 21 (58.3) | 43 (55.1) | 42 (58.3) | 22 (57.9) | 128 (57.1) |
| 12-<18 years | 13 (56.5) | 34 (73.9) | 27 (56.3) | 12 (60.0) | 86 (62.8) |
| Negative (all serotypes) | 42 (48.3) | 76 (42.0) | 83 (45.4) | 43 (47.8) | 244 (45.1) |
| 2-5 years | 17 (60.7) | 29 (50.9) | 32 (50.8) | 19 (59.4) | 97 (53.9) |
| 6-11 years | 15 (41.7) | 35 (44.9) | 30 (41.7) | 16 (42.1) | 96 (42.9) |
| 12-<18 years | 10 (43.5) | 12 (26.1) | 21 (43.8) | 8 (40.0) | 51 (37.2) |

Safety Conclusions (6 months)



- No safety signals detected
- No concerns identified based on solicited local AEs, solicited systemic AEs, unsolicited AEs
- No SAEs related to the investigational product or to trial procedures
- Acceptable and consistent with results from previous phase 1 and 2 studies

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Geometric Mean Titers (GMT) at 1 month – DENV-1

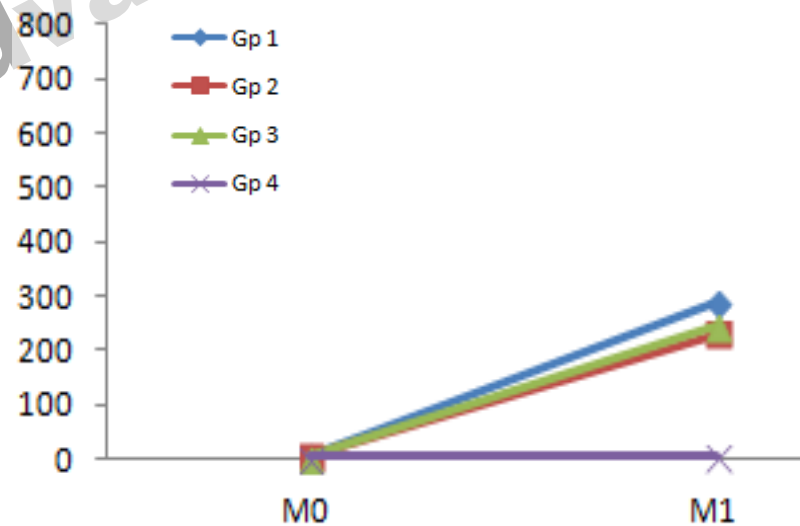
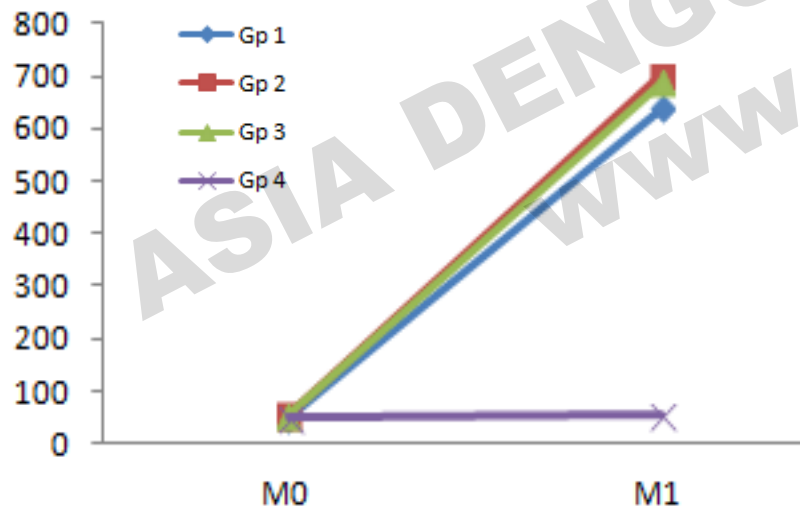


All subjects

| | Gp 1 (N=91) | Gp 2 (N=187) | Gp 3 (N=191) | Gp 4 (N=93) |
|----|----------------|-----------------|-----------------|----------------|
| M0 | 48.4 | 55.2 | 53.8 | 48.7 |
| M1 | 639.7 | 701.7 | 688.8 | 54.7 |

Seronegative at baseline

| | Gp 1 (N=42) | Gp 2 (N=76) | Gp 3 (N=84) | Gp 4 (N=43) |
|----|----------------|----------------|----------------|----------------|
| M0 | 5.0 | 5.0 | 5.0 | 5.0 |
| M1 | 286.8 | 229.5 | 245.7 | 6.3 |



Geometric Mean Titers (GMT) at 1 month – DENV-2

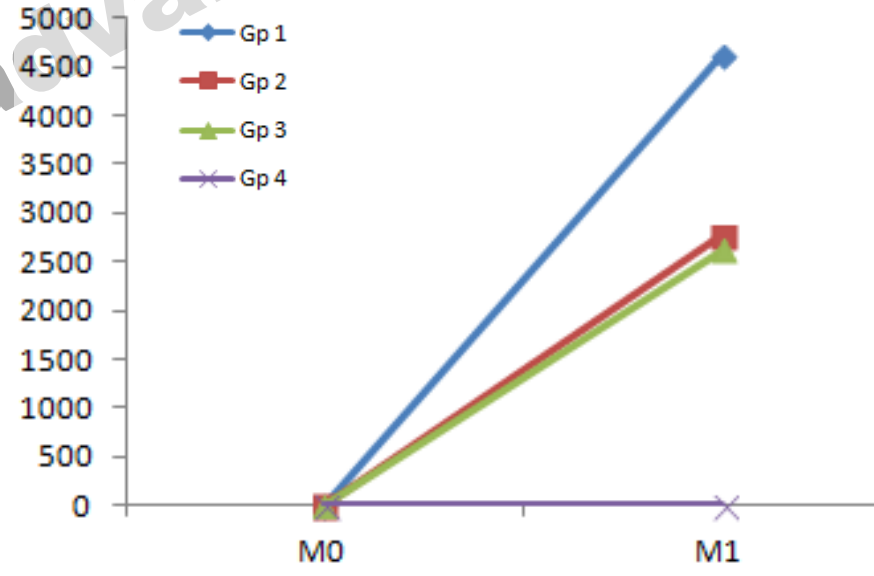
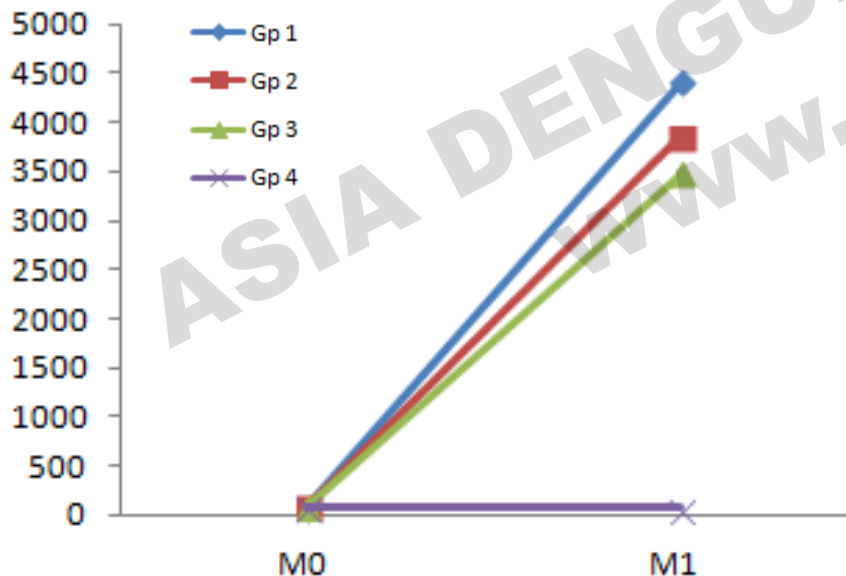


All subjects

| | Gp 1 (N=91) | Gp 2 (N=187) | Gp 3 (N=191) | Gp 4 (N=93) |
|----|----------------|-----------------|-----------------|----------------|
| M0 | 65.0 | 85.8 | 64.4 | 72.2 |
| M1 | 4408.4 | 3856.5 | 3471.2 | 66.9 |

Seronegative at baseline

| | Gp 1 (N=42) | Gp 2 (N=76) | Gp 3 (N=84) | Gp 4 (N=43) |
|----|----------------|----------------|----------------|----------------|
| M0 | 5.0 | 5.0 | 5.0 | 5.0 |
| M1 | 4626.3 | 2766.5 | 2626.6 | 6.3 |



Geometric Mean Titers (GMT) at 1 month – DENV-3

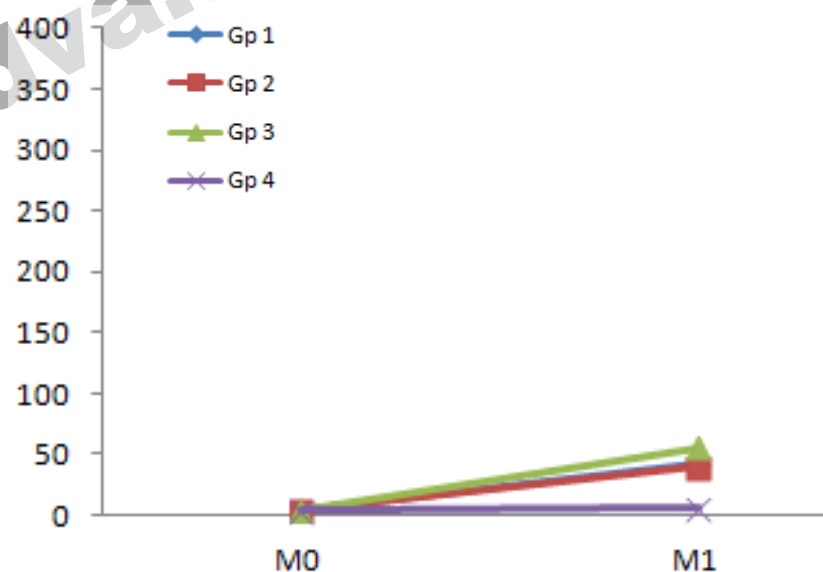
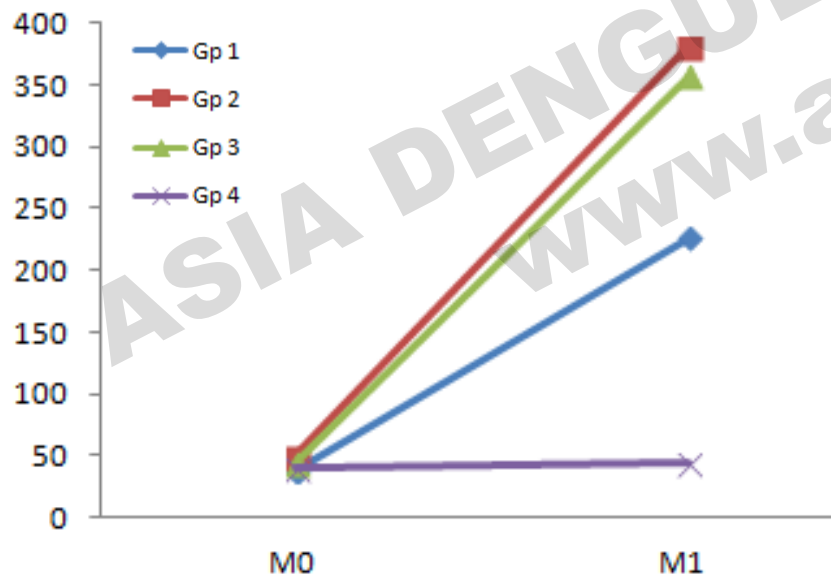


All subjects

| | Gp 1 (N=91) | Gp 2 (N=187) | Gp 3 (N=191) | Gp 4 (N=93) |
|----|----------------|-----------------|-----------------|----------------|
| M0 | 38.0 | 50.0 | 43.8 | 40.3 |
| M1 | 226.2 | 381.6 | 357.4 | 44.3 |

Seronegative at baseline

| | Gp 1 (N=42) | Gp 2 (N=76) | Gp 3 (N=84) | Gp 4 (N=43) |
|----|----------------|----------------|----------------|----------------|
| M0 | 5.0 | 5.0 | 5.0 | 5.0 |
| M1 | 41.7 | 39.7 | 55.9 | 6.7 |

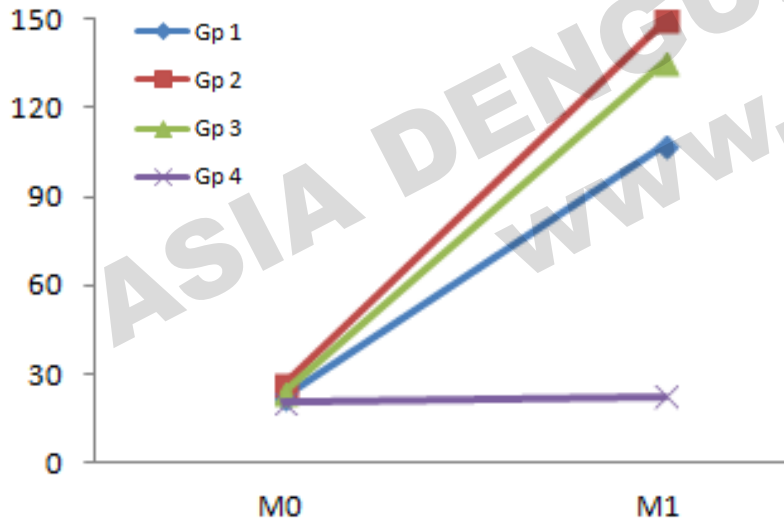


Geometric Mean Titers (GMT) at 1 month – DENV-4



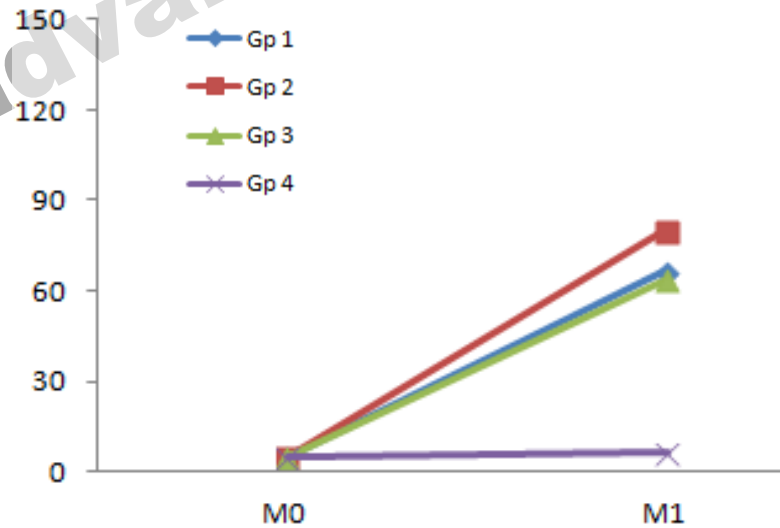
All subjects

| | Gp 1 (N=91) | Gp 2 (N=187) | Gp 3 (N=191) | Gp 4 (N=93) |
|----|----------------|-----------------|-----------------|----------------|
| M0 | 22.0 | 26.6 | 24.1 | 20.3 |
| M1 | 107.2 | 149.5 | 135.7 | 22.4 |

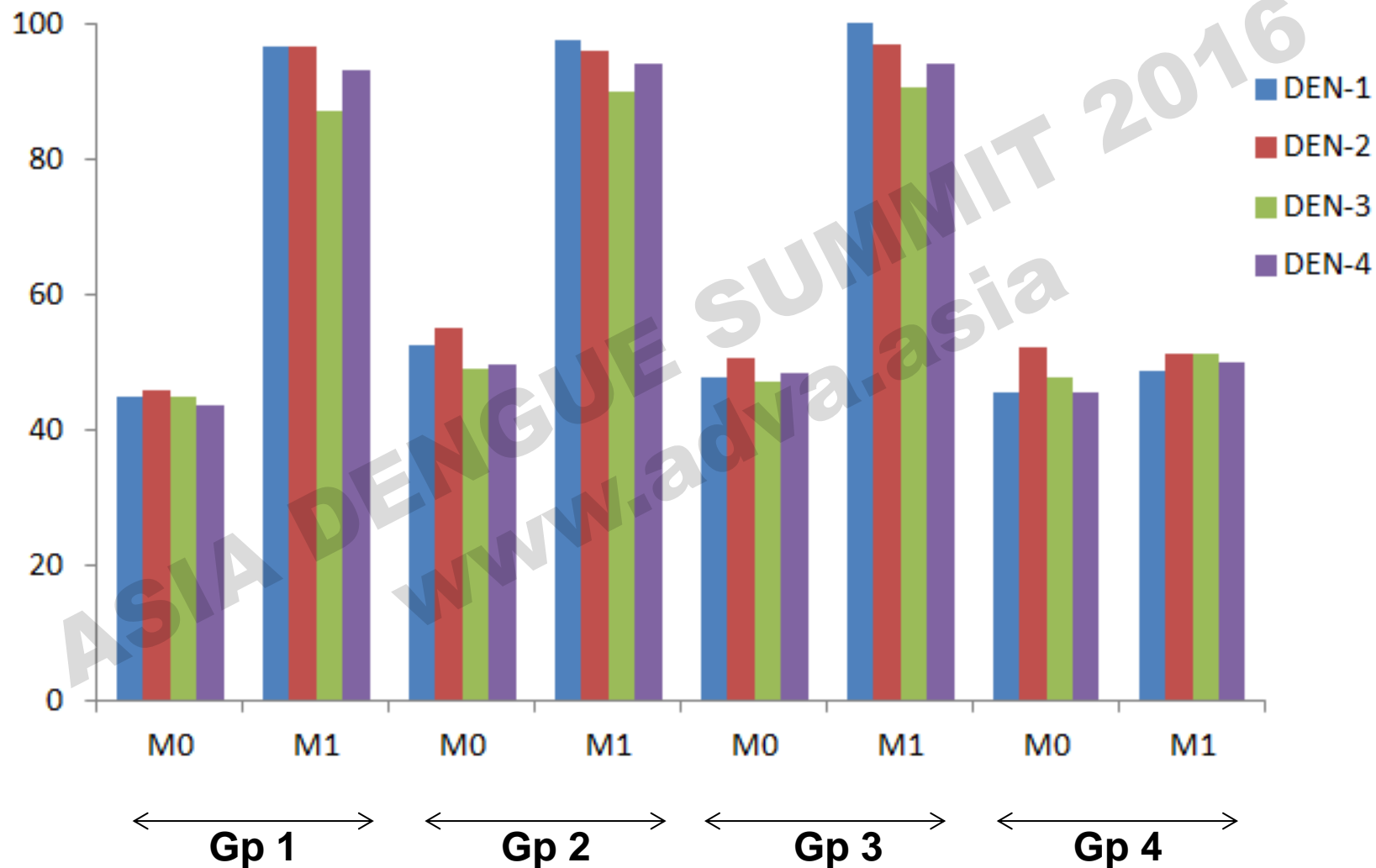


Seronegative at baseline

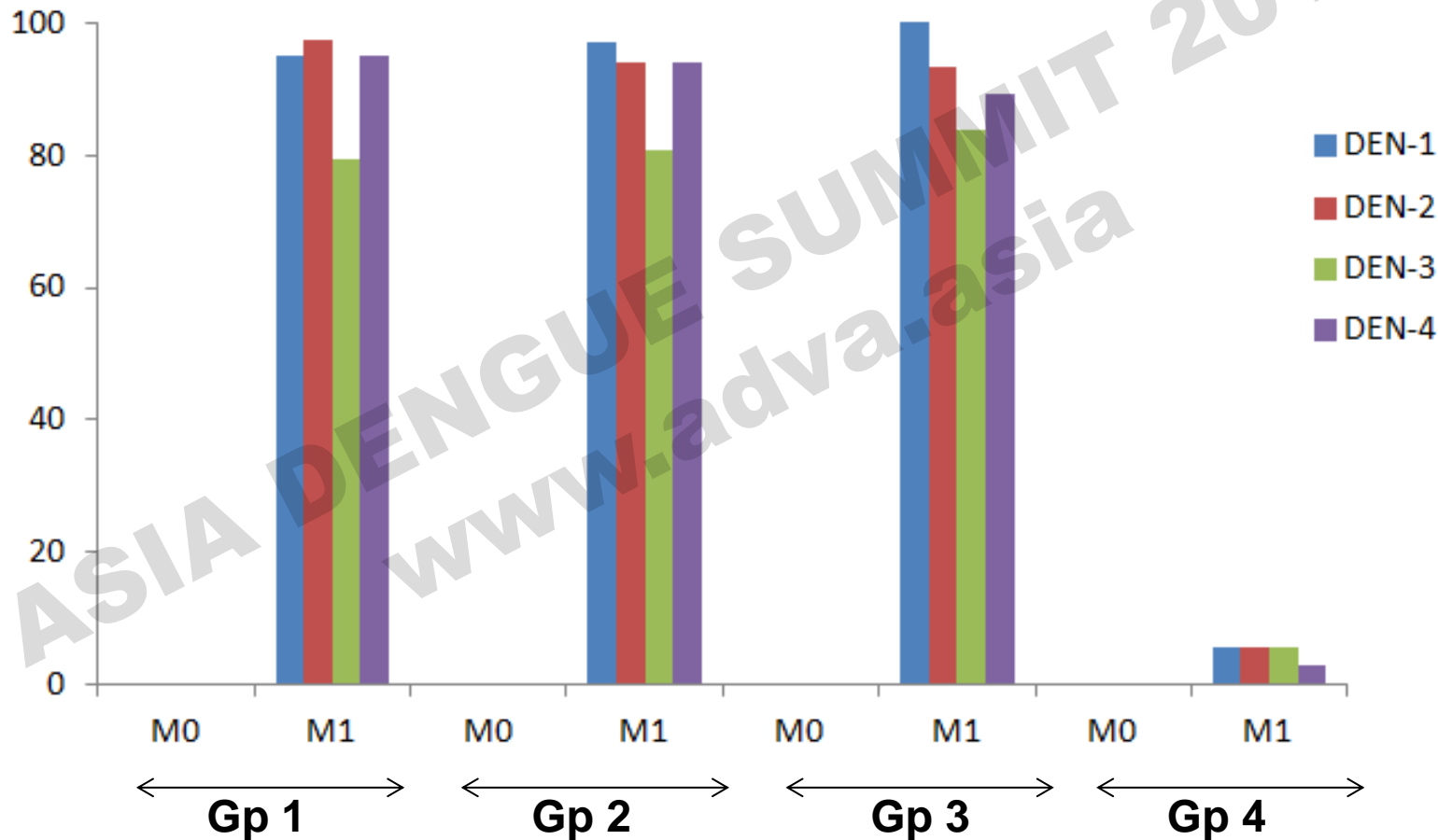
| | Gp 1 (N=42) | Gp 2 (N=76) | Gp 3 (N=84) | Gp 4 (N=43) |
|----|----------------|----------------|----------------|----------------|
| M0 | 5.0 | 5.0 | 5.0 | 5.0 |
| M1 | 66.8 | 80.4 | 64.2 | 6.4 |



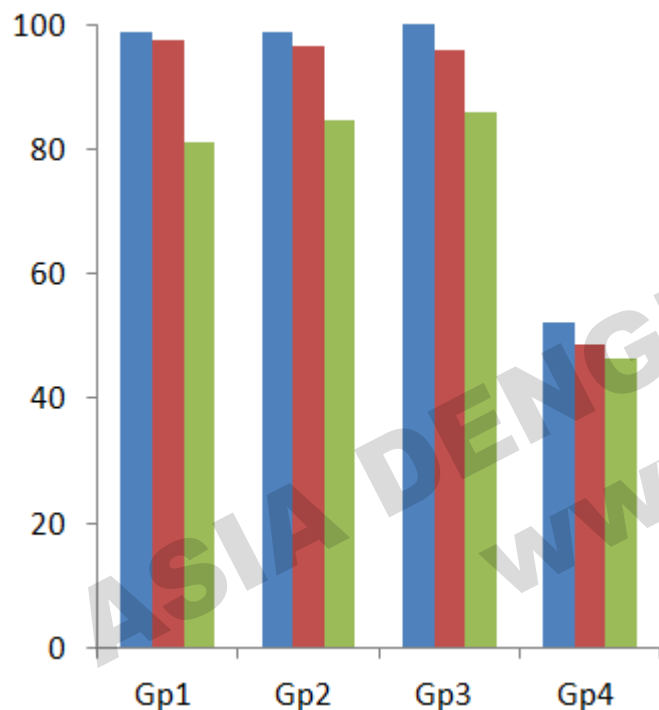
Seropositivity rate at 1 month – all subjects (immuno-subset)



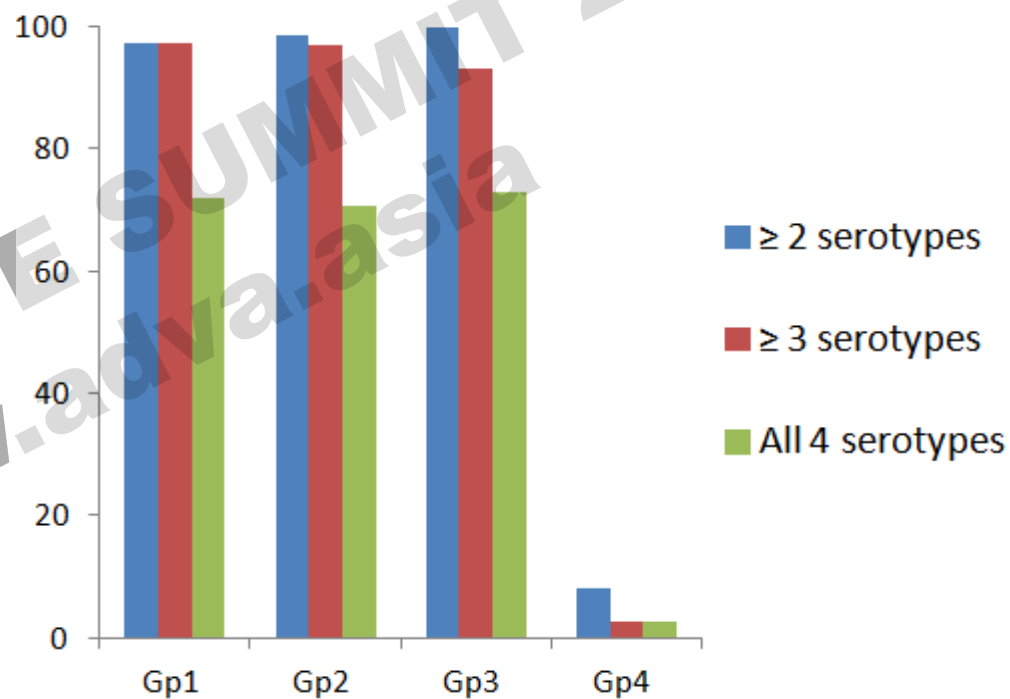
Seropositivity rate at 1 month – subjects (immune –subset) seronegative at baseline



Seropositivity rate to multiple serotypes at Month 1



ALL SUBJECTS



SERONEGATIVE AT BASELINE

Current Status: Subjects Enrolled in TDV Studies



| | TDV | Control | Total |
|----------|------|---------|-------|
| DEN 101 | 48 | 24 | 72 |
| DEN 102 | 79 | 17 | 96 |
| DEN 103 | 67 | 0 | 67 |
| DEN 104 | 136 | 0 | 136 |
| DEN 106 | 1002 | 0 | 1002 |
| DEN 203 | 249 | 111 | 360 |
| DEN 204 | 1596 | 198 | 1794 |
| DEN-205* | 250 | 0 | 250 |
| Total | 3427 | 350 | 3777 |

* Currently enrolling, Planned sample size of 400 in TDV groups

Thank you

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