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Immunogenicity and safety of concomitant and sequential administration of a yellow fever and tetravalent dengue vaccine: a phase 3 randomized, controlled study

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Background: There remains an unmet need for a dengue vaccine which can be administered irrespective of previous exposure. As dengue is often endemic in the same regions as yellow fever (YF), this phase 3 randomized controlled study evaluated the immunogenicity and safety of concomitant and sequential administration of a tetravalent dengue vaccine (TAK-003) with YF-17D vaccine in 18–60 year-olds (NCT03342898).

Methods: 900 participants were randomized 1:1:1 to receive the following on Days 1/90/180: YF-17D+placebo/TAK-003/TAK-003 (Group 1); TAK-003+placebo/TAK-003/YF-17D (Group 2); TAK-003+YF-17D/TAK-003/placebo (Group 3). The primary objective was non-inferiority (upper limit of 95% confidence interval [UL95%] of difference <5%) of YF seroprotection (neutralising titre ≥10) rate one month post-YF-17D co-administered with TAK-003 (Group 3) versus alone (Group 1). Secondary objectives included non-inferiority of YF and dengue geometric mean titres (GMTs) [UL95% for GMT ratio <2.0], and safety.

Results: One month after vaccination, co-administration of YF-17D and TAK-003 resulted in non-inferior YF seroprotection rate versus YF-17D alone (99.5% vs 99.1%; difference: 0.4% [−1.85 to 2.69%]). GMTs were non-inferior for YF (UL95% for GMT ratio: 1.26) and dengue serotypes DENV-2 (1.75), DENV-3 (1.61), and DENV-4 (1.46) but not DENV-1 (2.22). Rates of adverse events following TAK-003 were consistent with data from previous studies. No important safety risks were identified.

Conclusion: TAK-003 and YF-17D were immunogenic and well tolerated when concomitantly or sequentially administered. Non-inferiority of immune responses to both was demonstrated for concomitant administration, except against DENV-1, with lower titers compared to sequential vaccination, but similar to titers observed in other TAK-003 trials.

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