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Sponsor: Acambis **Drug substance(s):** CYD Dengue Vaccine	**Study Identifiers:** IND 10211 **Study code:** CYD01
Title of the study: A randomized, double-blind Phase 1 trial of the comparative safety, tolerability and immunogenicity of ChimeriVax™-DEN2, a live attenuated monovalent dengue 2 vaccine, and yellow fever 17D vaccine (YF-VAX®)	
Study center(s): One center in the US	
Study period: Date first subject enrolled: 05/Mar/2002 Date last subject completed: 26/Jun/2002	
Phase of development: Phase I	
Objectives: 1. The safety, tolerability and viremia levels following administration of ChimeriVax™-DEN2 at doses of 3.0 and 5.0 log10 plaque forming units (PFU) and a control vaccine (YF-VAX®) administered by the subcutaneous (SC) route to healthy adult male and female subjects. 2. The neutralizing antibody response against DEN2 in subjects vaccinated with ChimeriVax™-DEN2 at doses of 3.0 and 5.0 log10 PFU. 3. The effect of prior yellow fever (YF) immunity on immune response to ChimeriVax™-DEN2. 4. The duration of antibody response in subjects vaccinated with ChimeriVax™-DEN2 at doses of 3.0 and 5.0 log10 PFU.	
Methodology: This was a randomized, double-blind, controlled, single-center outpatient study in YF-naïve subjects. The study also comprised an open component in which antibody response to high dose ChimeriVax™-DEN2 vaccination was evaluated in YF-immune subjects. After screening, 42 eligible YF-naïve subjects were randomized equally to 3 groups (high or low dose ChimeriVax™-DEN2 or YF-VAX®). Initially 12 subjects were randomized, and since none of the discontinuation criteria were achieved after 3 weeks, the DSMB approved dosing of the remaining 30 YF-naïve subjects and the 14 YF immune subjects. On Day 1, subjects received a single SC vaccination with ChimeriVax™-DEN2 (high or low dose) or YF-VAX®. They returned to the clinic on Days 2-11, 21 and 31. Safety assessments were performed at specified time points during Days 1-31. Antibody responses to a wild-type strain of DEN2 and neutralizing antibodies to YF 17D and prototype strains of DEN 1- 4 were measured on Days 1 (pre-vaccination) and 31. The study was unblinded after completion of the treatment period, and subjects will be followed-up 6 and 12 months post-vaccination, to assess the durability of the antibody response. Data at 6 and 12 months are not presented in this report.	
Number of subjects/patients: Planned: 56 Randomized: 56 Treated: 56 **Evaluated:** Efficacy/Immunogenicity: 53 Safety: 56	

Diagnosis and criteria for inclusion:

Healthy adult subjects (18 to 49 years) who had not been previously vaccinated for YF (main study) or who had documented receipt of YF vaccine 6 months to 5 years prior to randomization (open-label study).

Study treatments

Investigational drug: ChimeriVaxTM-DEN2

Formulation: Partially purified virus suspension containing 8.1 log10 PFU/mL and was diluted with a solution containing minimal essential medium Eagle's salt (MEME) without phenol red or Lglutamine, and with 7.5% lactose and 2.5% human serum albumin, to provide doses of 5.0 or 3.0 log10 PFU.

Route of administration: SC injection (0.5mL)

Control: YF-VAX®

Formulation: formulated to contain not less than 5.04 log10 PFU/0.5 m dose. It was diluted with sodium chloride for injection USP

Route of administration: SC injection

Duration of participation: The maximum duration of participation for an individual subject is approximately 12 months.

Criteria for evaluation:

Safety:

Safety was assessed on the basis of adverse events (AEs, as assessed by spontaneous reporting, structured interview and subject diary), vital signs, physical examination, quantitative tests for viremia and routine laboratory investigations hematology, blood chemistry and urinalysis).

Immunogenicity:

Immunogenicity was assessed on the basis of neutralizing antibody response which was represented as the proportion of yellow fever non-immune subjects in the ChimeriVax™-DEN2 and YF-VAX® groups who seroconverted to WT strain 16681 (ChimeriVax™-DEN2) or the homologous virus (YF-VAX®) on Day 31 by plaque-reduction neutralization test (PRNT50). Day 31 DEN2 seroconversion was defined as the proportion of subjects who developed 50% neutralizing antibody titers ≥1:10. In the YF-VAX® group, seroconversion was defined as log10 neutralization index of ≥ 0.7.

Statistical methods:

All subjects who received at least one vaccination were included in the safety population. The Per Protocol (PP) population comprised all subjects who received at least one vaccination, provided baseline and Day 31 blood samples for antibody analysis and had no significant protocol deviations (identified prior to unblinding on a case by case basis).

Safety analysis:

AEs were coded using MedDRA Version 4.0 and tabulated by treatment group to show the number and percentage of subjects experiencing treatment emergent adverse events, both for all events and those considered possibly, probably or definitely related to treatment by the Principal Investigator. Treatment groups were compared for each of the viremia summary measures (peak, duration and area under the viremia vs. time curve) using an analysis of variance (ANOVA) model allowing for the effects of treatment and immune status. The difference between the groups in the proportion of subjects viremic on one or more study day was assessed by Fisher's Exact Test. Summary statistics were presented for vital signs, oral body temperature and clinical laboratory investigations, including changes from baseline.

Efficacy analysis:

Primary immunogenicity outcome:

The proportion of YF-naïve subjects in the high dose ChimeriVax™-DEN2 group and YF-VAX® groups who seroconverted to WT

strain 16681 (ChimeriVax™-DEN2) or the homologous virus (YF-VAX®) on Day 31 were compared using Fisher's Exact Test.

Secondary immunogenicity outcomes:

- The effect of dose response on the DEN2 seroconversion rate to WT strain 16681 on Day 31 was compared between ChimeriVax™-DEN2 high dose and low dose groups using Fisher's Exact Test.
- The effect of prior immunization with YF on the DEN2 seroconversion rate to WT strain 16681 on Day 31 in the YF-immune and YF-naïve groups receiving high dose ChimeriVax™-DEN2 was analyzed using Fisher's Exact Test.

Summary:

Population characteristics:

Fifty-six subjects, 14 per treatment group, were randomized, vaccinated and completed the 31-day follow-up. All 56 subjects were included in the safety population and 53 subjects, 14 in the 5.0 log10 PFU YF-immune group and 13 in each of the other treatment groups, were included in the PP population. Three subjects were excluded from the PP population due to prior YF immunity.

Safety:

All except 1 subject in the ChimeriVax™-DEN2 5.0 log10 PFU YF-naïve group reported AEs.

The profile of AEs following vaccination with ChimeriVax™-DEN2 was similar to that with YF-VAX®; nervous system disorders, gastrointestinal disorders, musculo-skeletal and connective tissue disorders and general disorders and administration site conditions were most commonly reported. Overall, the most frequent individual treatment-emergent AEs were headache (63%), myalgia (39%) and fatigue (29%). There was evidence to suggest a doseresponse relationship for ChimeriVax™-DEN2 in YF-naïve subjects with respect to the incidence of headache (79% with 5.0 log10 PFU vs. 43% with 3.0 log10 PFU), myalgia (50% vs. 36%) and fatigue (43% vs. 14%). A similar AE profile was reported for treatment-related AEs.

There were no SAEs. Six subjects, 1 YF-naïve subject in each treatment group and 3 YFimmune subjects receiving high dose ChimeriVax™-DEN2 developed a mild rash after vaccination. In 4 of the subjects who developed a rash (all 3 YF-immune subjects and 1 YFnaïve subject vaccinated with ChimeriVax™-DEN2 log10 3.0 PFU) the rash was considered by the investigator to be possibly related to the study treatment, however, all rashes were focal to the upper arm and unrelated to significant clinical symptoms. Five subjects had a total of 6 local injection site reactions (pain, redness and/or induration) following vaccination with YF-VAX®.

Most AEs were of mild to moderate intensity. One YF-immune subject had diarrhea that was considered definitely related to ChimeriVax™-DEN2. The time to onset of AEs was variable. In most subjects with headache (46%, 16/35) and myalgia (59%, 13/22), the event started more than 7 days after vaccination. Most AEs resolved within 1-4 days.

There was no obvious difference between the treatment groups with respect to the change in vital signs after vaccination. Nine subjects, 4 YF-naïve subjects in the ChimeriVax™-DEN2 high dose group and the YF-VAX® group, and 1 YF-immune subject in the ChimeriVax™-DEN2 high dose group had pyrexia reported as an AE. In 6 of these subjects (1 YF–naïve, 1 YF-immune subject vaccinated with ChimeriVax™-DEN2 high dose and all 4 YF-naïve subjects vaccinated with YF-VAX®) the pyrexia was considered possibly related to the study treatment. There were no obvious patterns for shifts in hematology, blood chemistry or urinalysis variables. Ten subjects, 4 YF-immune subjects (29%) in the ChimeriVax™-DEN2 high dose group and 2 YF-naïve (14%) each in the three treatment groups had abnormal laboratory values reported as AEs. All elevations of liver enzymes were minimal and unrelated to significant clinical symptoms.

The most commonly reported laboratory abnormality was increased CK (5/56 [9%] subjects). One report of increased CK in the ChimeriVax™-DEN2 5.0 log10 PFU YF-immune group was considered possibly related to the study treatment, though all were noted to be coincident with muscle strain or injury.

More YF-naïve subjects vaccinated with ChimeriVax™-DEN2 compared to YF-VAX® developed viremia: 8 (57%) in the ChimeriVax™-DEN2 5.0 log10 group; 8 (57%) in the ChimeriVax™-DEN2 3.0 log10 group compared with 2 (14%) in the YF-VAX® group. The proportion of subjects who developed viremia following vaccination with ChimeriVax™-DEN2 5.0 log10 PFU was slightly greater in YF-immune than in YF-naïve subjects (79% v 57%). The viremia mean peak (12.1 vs. 29.3 PFU/mL), duration (1.4 vs 1.9 days) and AUC (20.7 vs. 50.4 pfu/mL) following ChimeriVax™-DEN2 5.0 log10 PFU was greater in YF-immune subjects than that in YF-naïve subjects. While none of these values were statistically significant with this small sample,

the finding may be evidence of immune enhancement of ChimeriVax replication.

Efficacy:

Seroconversion rates to WT strain 16681 (DEN2) or the homologous virus (YF) were similar following vaccination of YF-naïve subjects with ChimeriVax™-DEN2 5.0 log10 PFU or YFVAX ® (100% vs. 92% respectively, p=1.00). There was no evidence of a dose-response relationship with respect to the seroconversion rate to WT DEN2 strain 16681 in YF-naïve subjects vaccinated with ChimeriVax™-DEN2 (100% with 5.0 log10 PFU vs. 92% with 3.0 log10 PFU, p=0.325). Prior YF immunization had no suppressive effect on seroconversion to WT DEN2 strain 16681 (100% seroconversion to WT DEN2 strain 16681 in both YF-naïve and YF-immune subjects receiving 5.0 log10 PFU ChimeriVax™-DEN2).

DEN Strain	Chimeri-Vax™-DEN2 5.0 log^{10} PFU YF- naïve	Chimeri-Vax™-DEN2 3.0 log^{10} PFU YF- naïve	Chimeri-Vax™-DEN2 5.0 log^{10} PFU YF-immune	p value (Fisher's Exact for difference between the groups)
16681	13/13 (100)	(12/13) 92.3	14/14 (100)	a
16007	3/13 (23.1)	3/13 (23.1)	14/14 (100)	<0.0001
01/481	0	0	0	-
16562	2/13 (15.4)	3/13 (23.1)	14/14 (100)	<0.0001
1036	0	0	100	<0.0001
Pr 159 American 1	12/13 (92.3)	11/13 (84.6)	14/14 (100)	0.3000
JaH American II	12/13 (92.3)	12/13 (92.3)	14/14 (100)	0.5333

a: p = 0.3250 for comparison Chimeri-Vax™-DEN2 5.0 log10 PFU YF-naïve & YF- immune vs Chimeri-Vax™-DEN2 3.0 log10 PFU YF-naïve; p = not calculable for Chimeri-Vax™-DEN2 5.0 log10 PFU YFnaïve vs Chimeri-Vax™-DEN2 5.0 log10 PFU YF-immune

There was no significant difference in geometric mean neutralizing antibody titers to WT DEN2 strain 16681 at Day 31 in YF-naïve subjects vaccinated with 5.0 log10 PFU or 3.0 log10 PFU ChimeriVax™-DEN2 or YF-immune subjects vaccinated with 5.0 log10 PFU ChimeriVax™-DEN2 (geometric mean neutralizing antibody titres 358.6, 365.0 and 383.3 for ChimeriVax™-DEN2 5.0 log10 PFU YF-naïve, ChimeriVax™-DEN2 3.0 log10 PFU YF-naïve and ChimeriVax™-DEN2 5.0 log10 PFU YF-immune, respectively; ANOVA for overall difference between the groups p =0.9900).

High neutralizing antibody titers to DEN2 strains 16681, ChimeriVax™-DEN2, PR-159 and JaH were recorded in all treatment groups, with serotype specific responses to WT DEN2 strains in YF-naïve subjects observed. In YF-immune subjects, a broader cross-reactive response to the other DEN serotypes (1, 3 and 4) was recorded. This cross-reaction to other dengue serotypes was not observed among YF-naïve subjects. None of the YF-naïve subjects vaccinated with ChimeriVax™-DEN2 seroconverted to YF.

100% of subjects vaccinated with ChimeriVax™-DEN2 seroconverted to the homologous strain; however, geometric mean neutralizing antibodies were significantly higher in the higher dose group.

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