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Innovations to accelerate vaccine development and manufacture

Workshop On Refining The Regulatory Context Of Controlled Human Infection Models

To use a CHIM, yes or no?

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Types of CHIMs

- Disease Models: Induce clinical illness as the primary endpoint of the study
  - Used primarily for mucosal pathogens as shedding of pathogen is not a useful endpoint
  - Examples include enteric pathogens (Shigella, Salmonella, Cholera, ETEC, Campylobacter) and respiratory pathogens (RSV, influenza)
- Infection Models: Recovery of the pathogen is the primary endpoint (malaria is the prototypic model)
  - Model may have symptoms, but symptoms are generally mild (dengue, Zika)

Purpose of a CHIM

- Down-selection of candidate vaccines/therapeutics
- Evaluate the protective efficacy of candidates in small trials to choose best candidate to move forward in large phase II and phase III clinical trial
- Contribute to the regulatory approval of candidate vaccines if traditional phase III clinical trials cannot be done (sporadic epidemics, incidence of pathogen)
- Learn more about specific pathogens
- Evaluation of correlates of protections

Use of challenge model for vaccine licensure

- Cholera vaccine
  - The live attenuated cholera vaccine Vaxchora (PaxVax) was licensed based on efficacy data from the cholera CHIM
  - CHIM was critical because:
    - ***The low incidence of cholera infection in travelers made a traditional field efficacy trial non-feasible***
    - The trial established an immunologic correlate of protection that could be used as a regulatory criterion for immunologic bridging.
- Efficacy of Typbar-TCV conjugated Salmonella vaccine
  - Assessed in a controlled human typhoid infection model in naïve-adult volunteers in the UK.
  - Supported pre-qualification by WHO

CHIMS for product development

- Must have well-defined, relevant endpoints to drive decision-making
  - Which strains are chosen and which type of model will determine what these endpoints are
  - Endpoints should be reproducible and occur with relative high frequency to reduce sample size needed
  - Discussions of these endpoints early on with regulators is a must
- Strain chosen for CHIM should be relevant for strains currently circulating/regions where product will be deployed

Advantages of challenge models

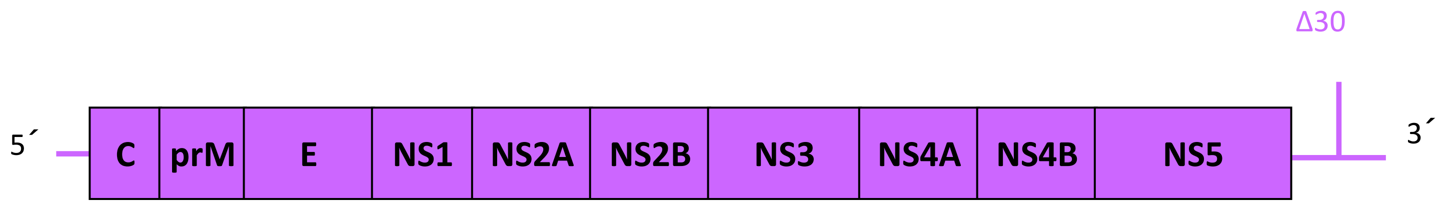
- If the model induces a reproducible endpoint of high-enough incidence, challenge studies can be powered with relatively small numbers of volunteers
  - Phase 3 efficacy studies generally assume an incidence of infection <1%, requiring large numbers of volunteers to be enrolled to acquire enough cases for efficacy determination
    - Incidence of natural infection may be seasonal or sporadic delaying the accumulation of cases for endpoint analysis
    - Challenge models can have infection/disease incidence of 60 – 100%
  - All volunteers are infected over a short duration of time
- ***Note: Phase 3 trials must still be conducted to evaluate vaccine safety***

CHIM use for product development – the dengue experience

- Phase 2b trial demonstrated that neutralizing antibody titers are not predictive of protection against dengue
- Developed dengue CHIMs to better assess potential efficacy of the NIH live attenuated tetravalent dengue vaccine TV003 prior to large trials in dengue endemic areas
  - Establish which formulation should move to phase 3
- Utilized the CHIM to study the immuno-protective and possibly immunopathology of DENV infection
  - ? Find correlate(s) of protection/risk

DENV-2 CHIM

- Developed from DENV-2 Tonga/74 virus that was described as a naturally attenuated DENV (caused milder illness, lower viremia outbreak in Kingdom of Tonga)
  - Tonga/74 is different DENV-2 genotype (American) than strain in TV003 vaccine (Asian)
- DHIM developed using a DENV-2 virus initially developed as a vaccine candidate but failed in preclinical evaluation
  - DEN2Δ30 was not attenuated in NHP studies

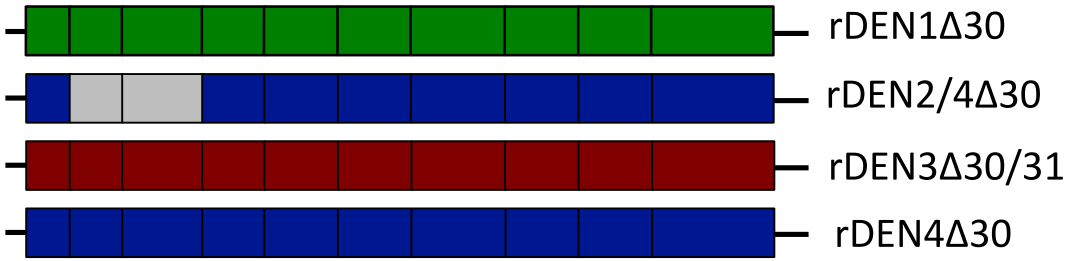


DENV-2 CHIM

- Induced viremia in 100% of subjects
  - Viremia easily measured (100-fold higher than LLQ)
- Induced clinical signs and symptoms consistent with DENV infection
  - Rash in 80% of subjects (50% moderate intensity)
  - Neutropenia in 40% of subjects
    - Moderate in 2 subjects (ANC nadir = 500-749/mm3)
    - Mild in 2 subjects (ANC nadir = 750-999/mm3)
- **No subject developed fever, elevated LFTs, or signs vascular leak**

DENV-2 CHIM to evaluate efficacy of LATV dengue vaccine

- 2 formulations of live attenuated tetravalent dengue vaccine were identified: TV003 and TV005
- Only difference in the 2 formulations was the dose of the DENV-2 component
  - TV003: each component given at 10^3 PFU
  - TV005: DENV-1, DENV-3, DENV-4 components given at 10^3 PFU, DENV-2 component given at 10^4 PFU
- DENV-2 component is chimeric and is more attenuated



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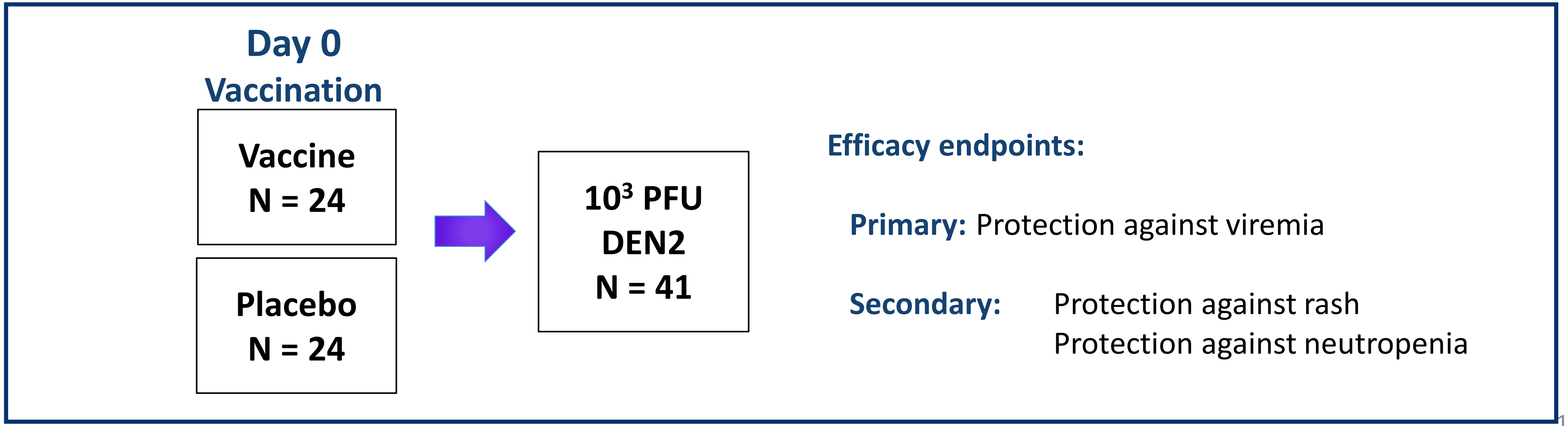
Neutralizing antibody responses to TV003 & TV005

		% seroconverted ($PRNT_{50} \geq 10$)				Mean peak titer (GMT)			
Vaccine	N	**DEN1**	**DEN2**	**DEN3**	**DEN4**	**DEN1**	**DEN2**	**DEN3**	**DEN4**
TV003	38	92	76	97	100	63	39	83	144
TV005	39	92	97	97	97	35	91	100	205

		Multivalent antibody response (cumulative)			
Vaccine	N	**Tetra**	Tri	Bi	Mono
TV003	38	**74**	24 (98)	2 (100)	0
TV005	39	**90**	8 (98)	0	2 (100)

DENV-2 CHIM used to evaluate protective efficacy of TV003

- Flavivirus-naïve volunteers 18 – 50administered a single dose of TV003
- 6 months later challenged with 1,000 PFU rDEN2Δ30
- **Primary efficacy endpoint is protection against viremia with rDEN2Δ30 (60% efficacy at a power of 0.8)**
  - If only powered for viremia, only needed 10 in each group



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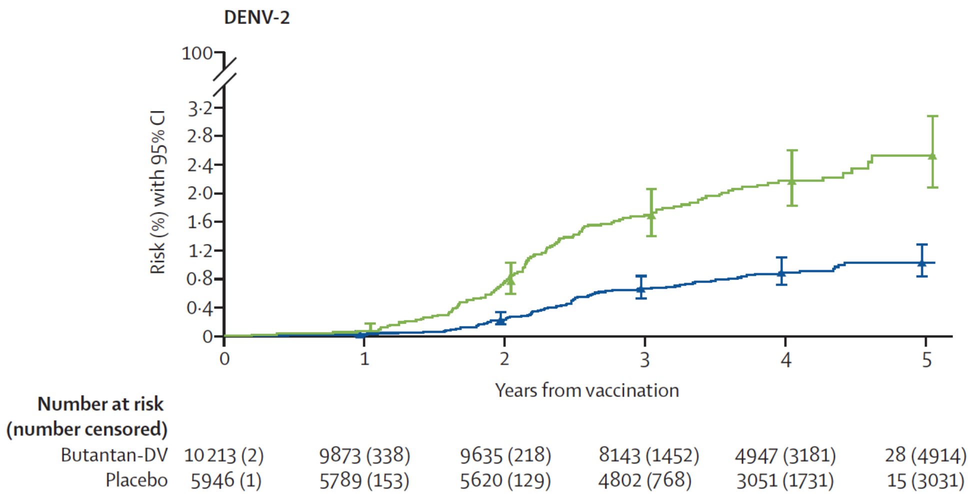
TV003 completely protected against challenge at 6 months

Adverse event	Post-challenge: Placebo recipient (n=20)	Post-challenge: TV003 recipient (n=21)	p-value
Viremia	**100.0%**	**0.0%**	**<0.0001**
Systemic:			
Fever	0.0%	0.0%	n/a
Headache	23.8%	25.0%	1.0000
Rash	**80.0%**	**0.0%**	**<0.0001**
Neutropenia	**20.0%**	**0.0%**	**0.0478**
Elevated ALT	5.0%	0.0%	0.4878
Myalgia	20.0%	4.8%	0.1836
Arthralgia	5.0%	0.0%	0.4878
Retro-orbital Pain	25.0%	9.5%	0.2379

TV003 phase 3 clinical trial – efficacy through 2 years & beyond

	Overall efficacy	DENV-1	DENV-2
Overall	**79.6** (70.0-86.3)	**89.5** (78.7-95.0)	**69.6** (50.8-81.5)
Seropositive	**89.2** (77.6-95.6)	**96.8** (81.0-99.8)	**83.7** (63.1-93.5)
Sero-naive	**73.6** (57.6-83.7)	**85.5** (61.1-94.0)	**57.9** (20.8-78.1)

Kallas, NEJM2024



Nogueira, Lancet Infect Diseases 2024

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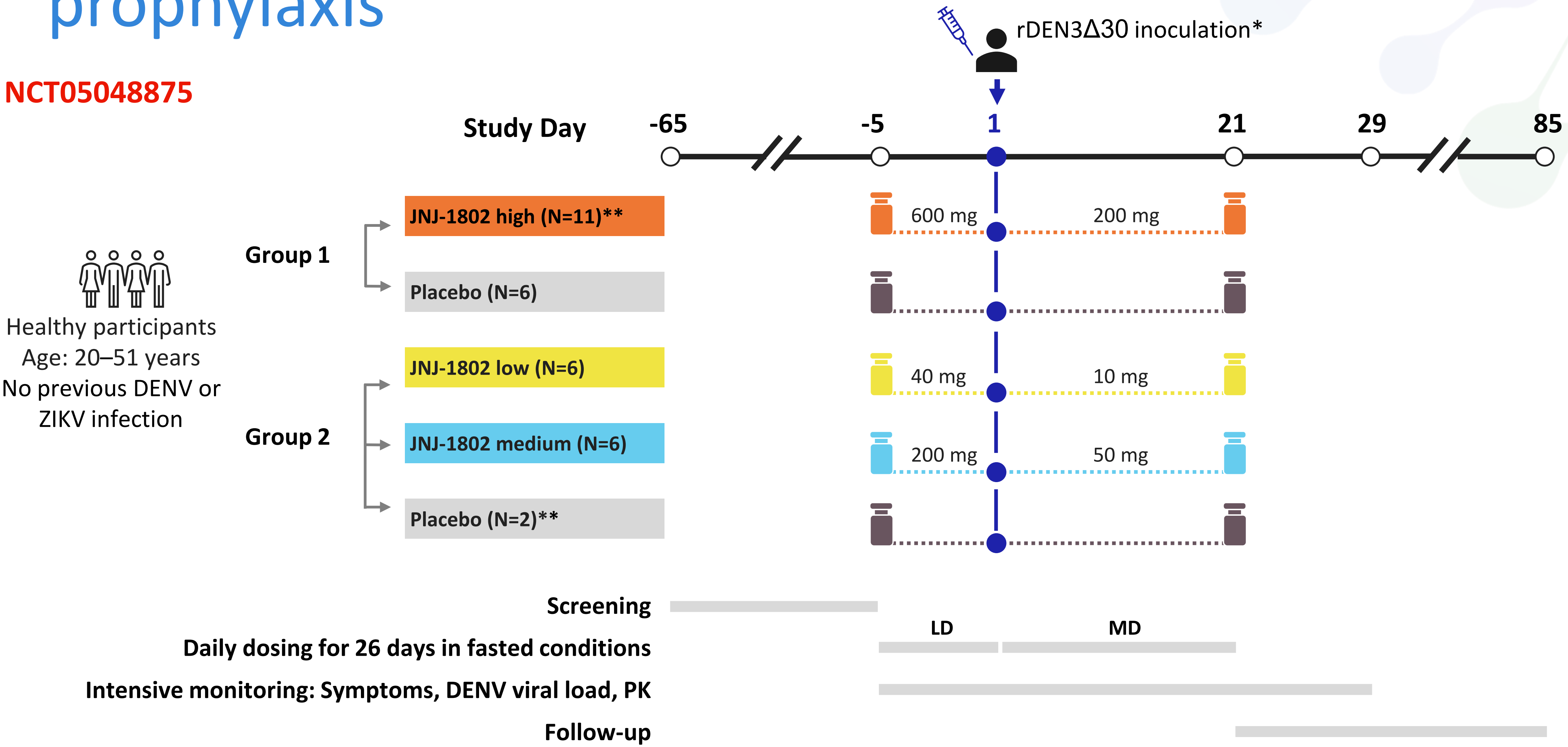
Phase 2a DENV-3 challenge study: pre-exposure prophylaxis

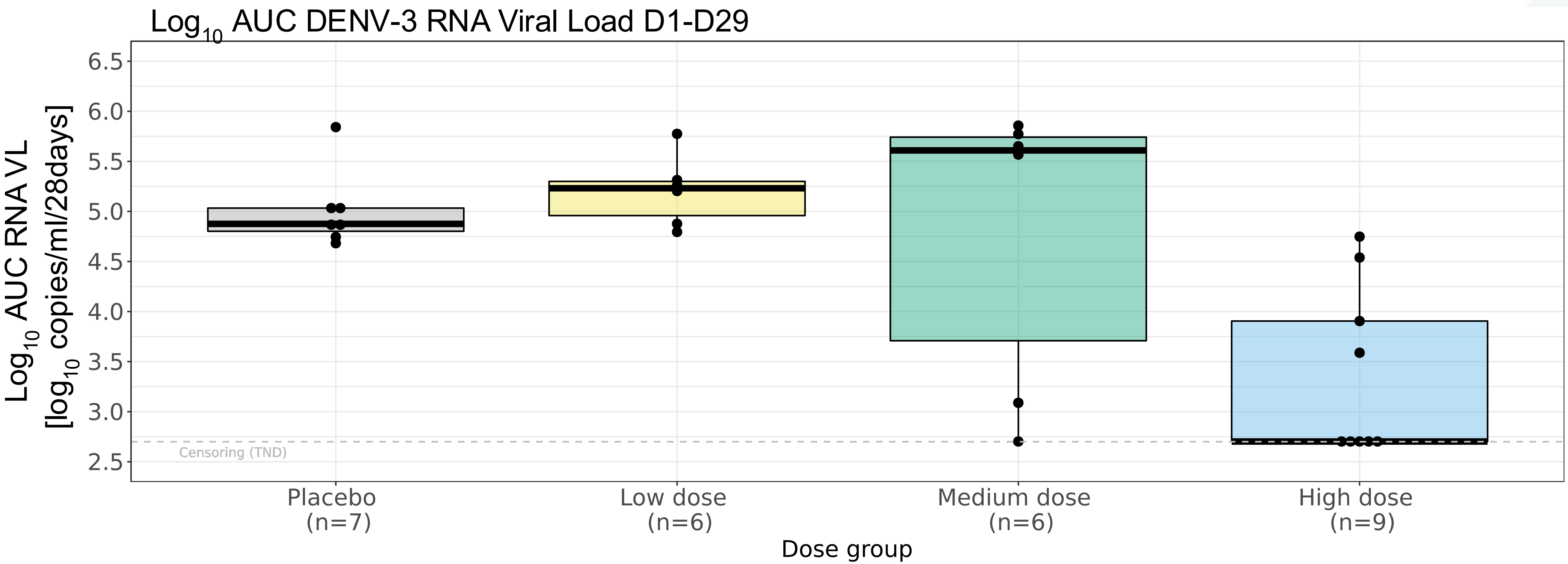
NCT05048875



Study Objectives and endpoints

- **Primary objective**: assess the antiviral activity of JNJ-1802 (high dose) versus placebo in terms of reduction of DENV-3 RNA
- **Primary endpoint**: Area under the DENV-3 RNA viral load (VL) concentration-time curves (AUC) from immediately before inoculation (baseline on Day 1) until Day 29 (AUCD1-D29 [VL])
- Secondary endpoints: Virology endpoints, including:
  - Peak, duration, and time to first onset of detectable DENV-3 RNA
  - Viremia (infectious virus) over time
  - Antibody response in terms of anti-DENV IgG and IgM
  - DENV-infection associated adverse events (solicited systemic AEs)
  - Safety
  - Pharmacokinetics (PK)

AUC DENV-3 RNA viral load by dose



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DENV CHIM

- Very useful in selection of candidate vaccine formulation to move forward
- Efficacy in CHIM higher than Phase 3 trial
  - Challenge at 6 months vs through 2 years
  - Dose of challenge strain and method of administration different from wild-type infection
- Established proof-of-concept for dengue anti-viral development
- Currently evaluating DENV monoclonal antibody as treatment and prophylaxis for dengue

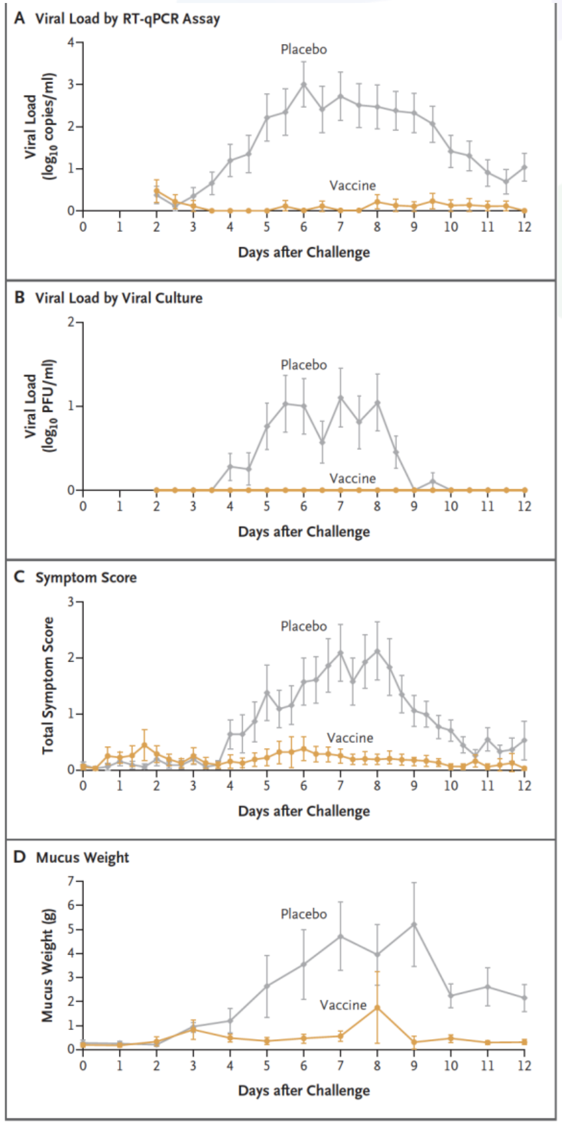
RSV CHIMs

Desirable RSV strain characteristics

- The strain should be contemporary
  - 2007 RSV A Memphis-37
  - 2011 RSV A/Maryland/001/11
- Should be representative of clinical strains that are circulating
- Known disease symptoms/severity of disease
- Documentation of method of isolation and production
- Propagation history
- Growth characteristics defined in invitro cell systems and human airway systems
- Wide availability/accessibility

RSV-CHIM proof of concept for vaccine development

- A phase 2b single center randomized-double blind study
- 70 adults 19 – 50 were randomized 1:1 to receive 120 µg of RSV-preF vaccine or placebo
- 28 days after infection participants were challenged IN with 4.5 log_{10} PFU of RSV A Memphis 37b
- Primary endpoints were
  - RSV-qPCR-confirmed detectable RSV on ≥ 2 consecutive days with ≥ 1 clinical symptom of any grade from 2 categories or ≥1 Grade 2 from any category
  - AUC RSV viral load from day 2 post-challenge to discharge



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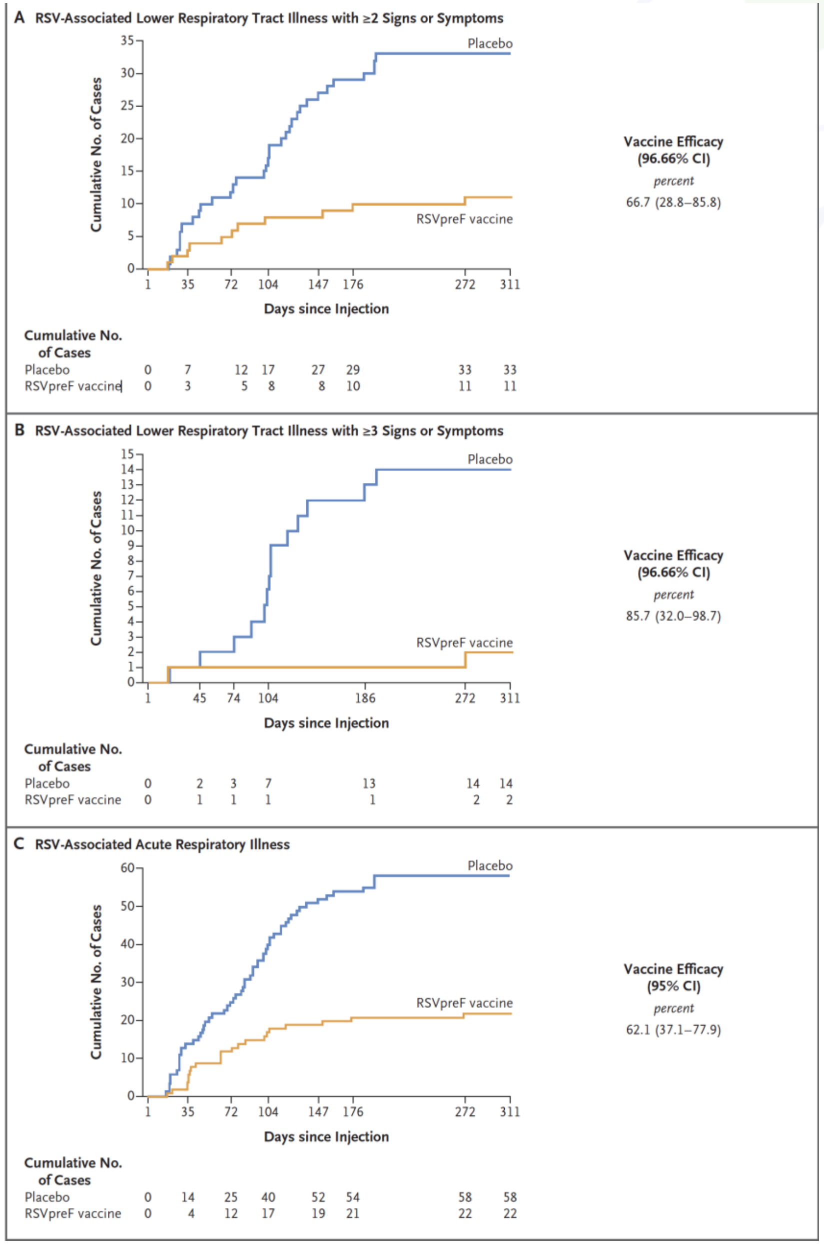
Efficacy results of RSVpreF in CHIM

- Efficacy of RSVpreF against symptomatic RSV infection confirmed by any detectable viral RNA on at least 2 consecutive days was **86.7% (95% CI, 53.8– 96.5)**
- 2/31 participants (6%) in the RSVpreF group developed symptomatic infection after challenge compared with 15/31 (48%) in the placebo group
- Supported further development of vaccine in Phase 3 clinical trial

CHIM vs Phase 3 trial

- Phase 3 efficacy trial of RSVpreF conducted in adults ≥60 years of age randomized 1:1 to receive RSVpreF 120 µg or placebo
- 2 primary endpoints
  - Protection against seasonal RSV-associated LRT illness with ≥ 2 or ≥3 signs or symptoms
  - Efficacy against RSV-associated acute respiratory illness



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RSV A CHIM summary

- RSV A CHIM well-established with different contemporary strains to choose from
- RSV A CHIM has been used to evaluate vaccine candidates prior to Phase 3
- RSV A CHIM results correlated well with Phase 3 clinical trial
  - Did not distinguish RSV A illness from RSV B illness
- The model has been proven to be useful for product development and correlated well with field studies
  - Important tool for additional product development
- Possible use in better characterization/identification of immune correlates

Summary

- CHIMS can be very useful in the identification/down-selection of prophylactic and therapeutic products
- The CHIM must have relevant and reproducible outcomes that occur with high enough frequency to provide an advantage in the development pathway
- The primary and secondary endpoints of clinical trials must be carefully designed to ensure the CHIM study will provide meaningful data
- Efficacy or effectiveness trials in CHIMs may differ in “real-world” studies but critical go-no go decisions can be made with CHIMs