

Viral kinetic modeling of mosnodenvir prophylaxis against DENV-3 in a controlled human infection model

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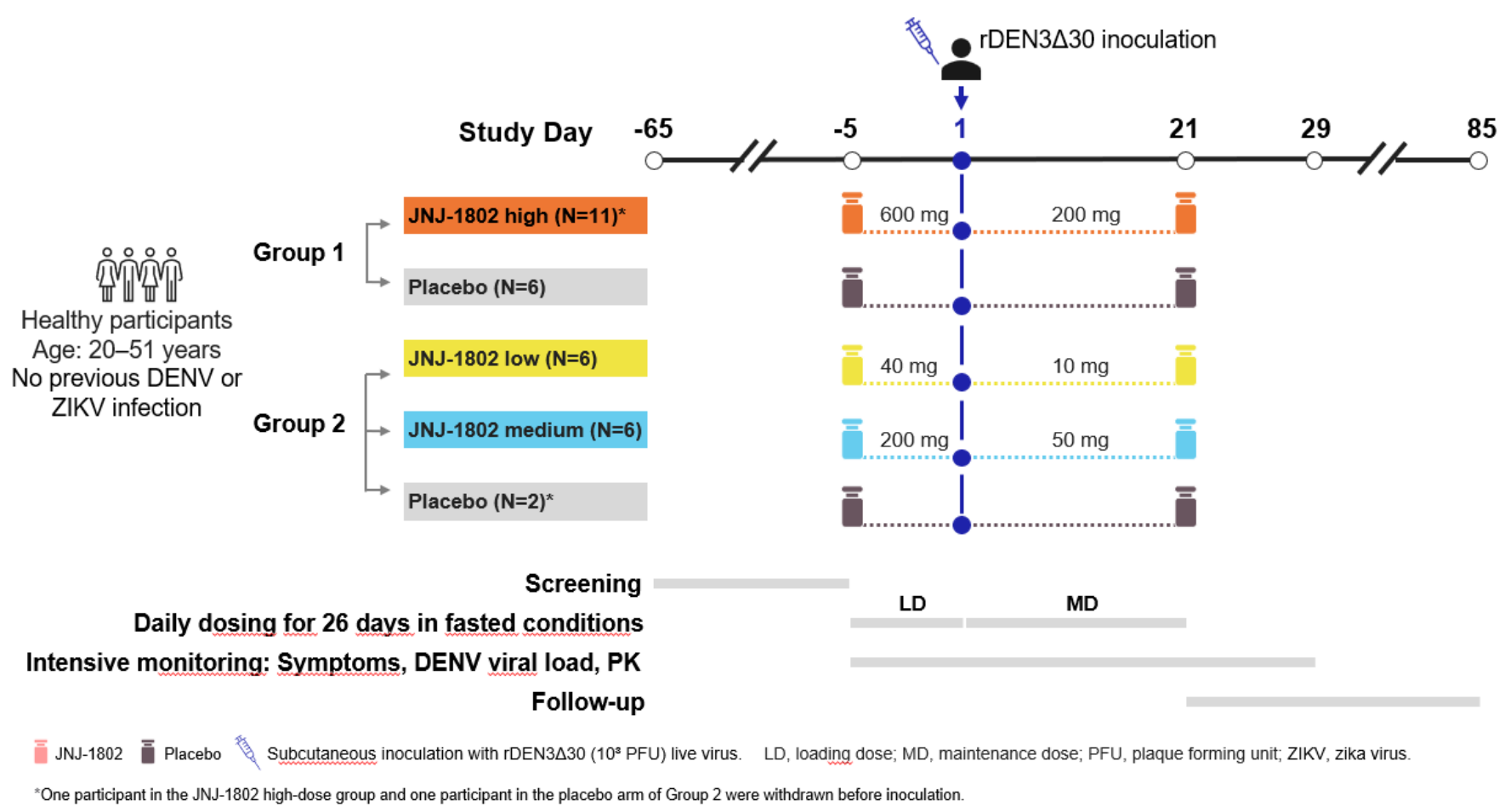
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Introduction

- Dengue virus (DENV) infection is transmitted to humans through the bite of infected mosquitoes and caused by any of the **four virus serotypes** (DENV-1 to DENV-4).
- About half of the world's population is at risk of dengue with an estimated 100–400 million infections occurring each year [1]. While many dengue infections are asymptomatic, a small fraction can progress to severe disease or even be fatal. Currently, there is **no DENV-specific treatment** available.
- Mosnodenvir (JNJ-64281802) is a pan-serotype dengue antiviral small molecule in clinical development that **blocks viral replication** by inhibiting de novo interactions between DENV nonstructural (NS) proteins NS3 and NS4B [2].
- A Phase 2a study (NCT05048875) evaluated the antiviral activity, safety and PK of daily oral doses of mosnodenvir as prophylaxis against DENV-3 infection in a **controlled human infection model (CHIM)**, under a loading-maintenance dose regimen: high, medium or low dose in Cohort 1 (C1, Figure 1).

Figure 1. Phase 2a CHIM study design (Cohort 1)



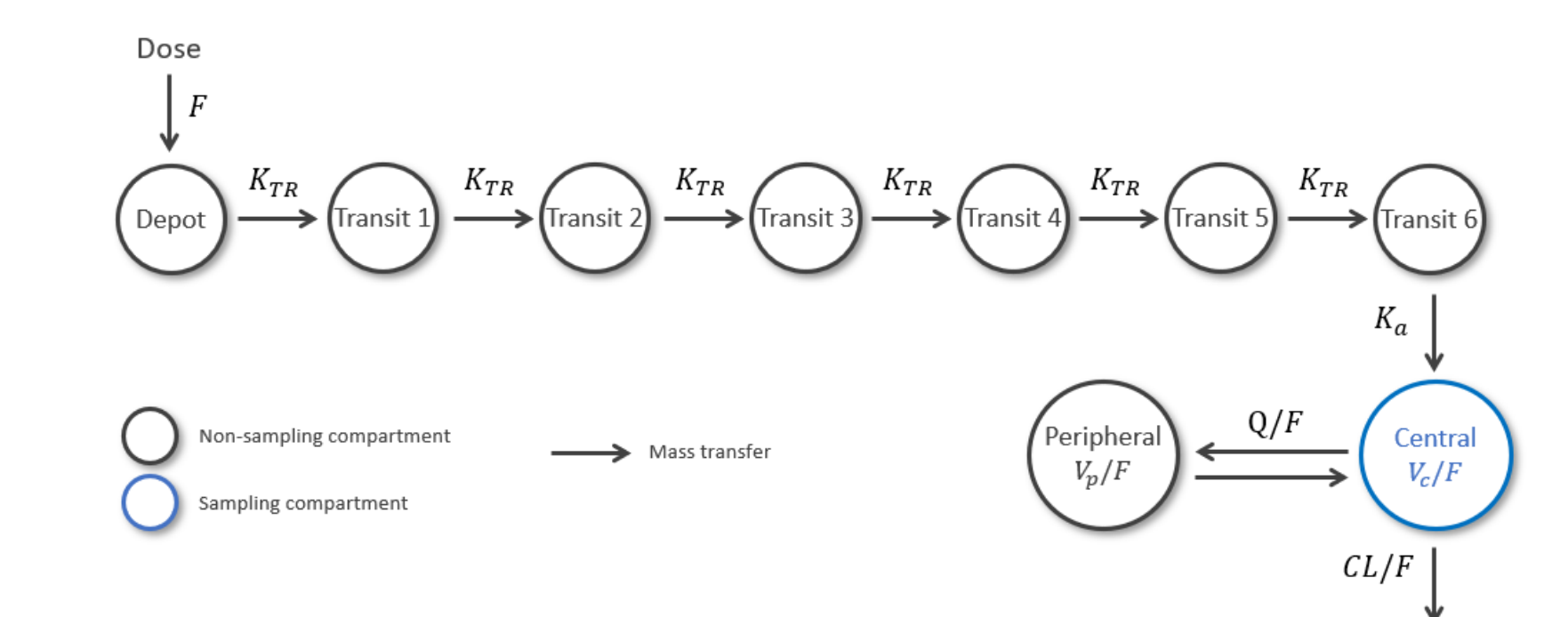
Objectives

To estimate the **prophylactic effect** of mosnodenvir against DENV-3 in a CHIM using a combined population PK (PopPK) and **viral kinetic model (VKM)**, and to **inform dose selection** for a subsequent cohort of the same study using model-based simulations.

Methods

- A **PopPK model** for mosnodenvir was developed based on plasma PK data from three Phase 1 studies and Cohort 1 of the Phase 2a study, including single- and multiple-doses administered daily or (twice) weekly.
- The target cell-limited [3] and immune response model [4] were considered as **VKMs** to describe the observed DENV-3 RNA levels in the CHIM, using a stepwise approach:
 - Building VKM for participants on placebo
 - Extending VKM with individual PopPK model estimates to capture the prophylactic effect of mosnodenvir.
- Based on the final PK-VKM, 500 study replicates with N=6 participants per dosing arm were **simulated** for different dose regimens. Simulated exposure and antiviral activity metrics were compared to guide dose selection for Cohort 2.
- Software:** NONMEM version 7.4 for PopPK model fitting (FOCE-I), VKM fitting (Laplace, M3) and PK-VKM simulations. R version 3.6.2 or higher for PopPK model simulations.

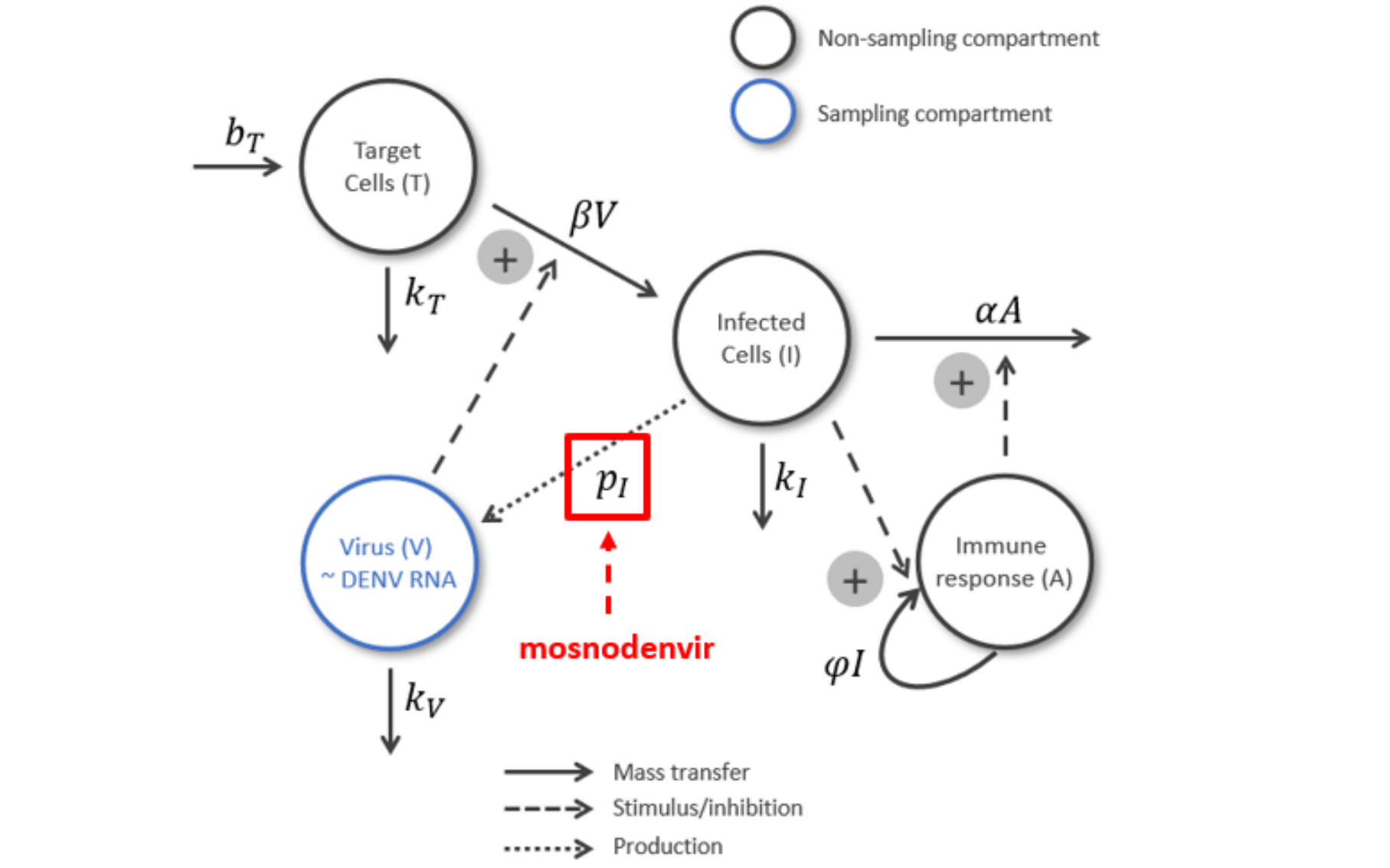
Figure 2. Mosnodenvir PopPK model



Results

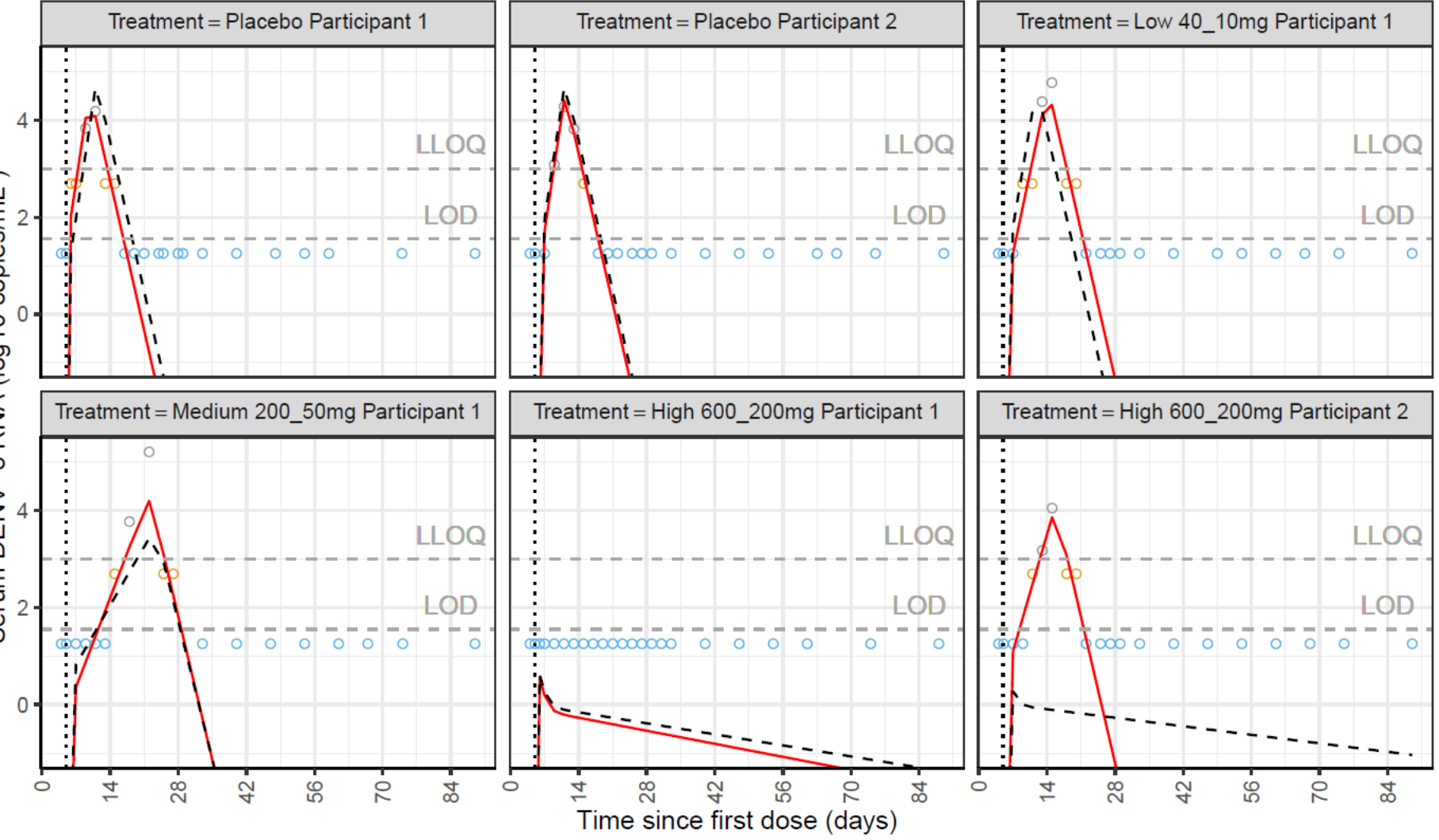
- The **PopPK model** for mosnodenvir was developed based on 8,352 plasma PK samples from 246 healthy participants.
- Mosnodenvir PK was adequately described by a **two-compartment** model with a food-, dose-, and formulation-dependent delayed first-order absorption, and first-order elimination (Figure 2). A covariate effect of BMI was included on F, Ka and CL/F.

Figure 3. PK-VKM for mosnodenvir in the CHIM study Cohort 1



- The **PK-VKM** was developed on RT-qPCR data from 602 serum samples from 29 participants in the CHIM C1, receiving placebo or one of the three mosnodenvir dose regimens.
- The final PK-VKM is an **immune response model** with mosnodenvir antiviral effect on the virion production rate (Figure 3), assuming a sigmoid E_{max} relationship with the average mosnodenvir concentration at steady state (C_{avg,SS}).
- The final PK-VKM adequately described the observed DENV-3 RNA course for all dose regimens (Figure 4).

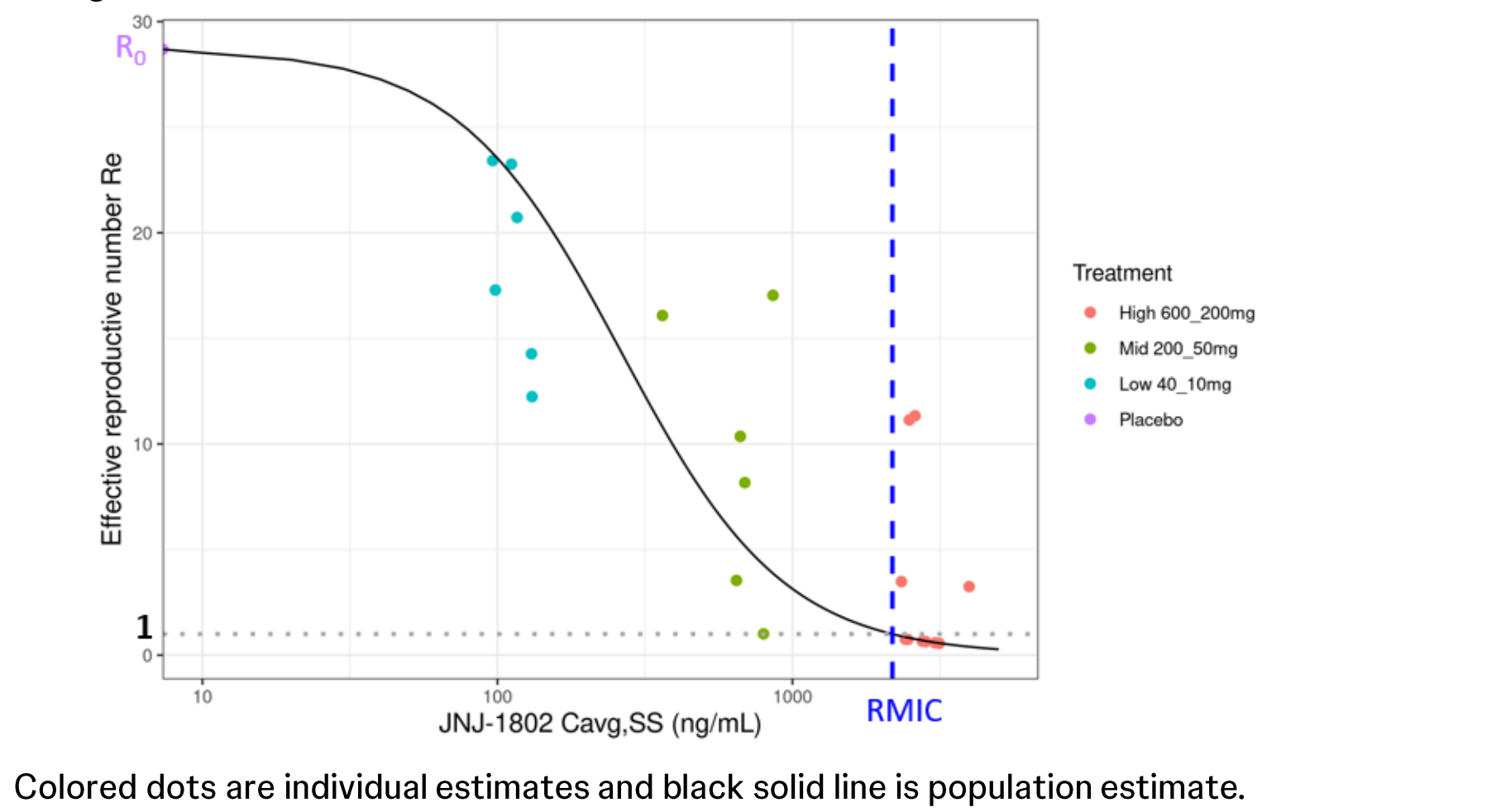
Figure 4. PK-VKM individual fit for random selection of participants in the CHIM study Cohort 1



Gray circles are detectable DENV-3 RNA $\geq$ LLOQ (1000 copies/mL), orange circles detectable DENV-3 RNA $<$ LLOQ and blue circles undetectable DENV-3 RNA (LOD 36 copies/mL). Red solid lines are individual estimates and black dashed lines are population estimates.

- The basic reproductive number **R₀**, ie, the average number of secondary infections caused by a single infected cell over its lifespan within the host, was estimated 28.7 cells (Figure 5).
- The reproduction minimum inhibitory concentration **RMIC** for mosnodenvir was estimated as C_{avg,SS} of 2,180 ng/mL [5].

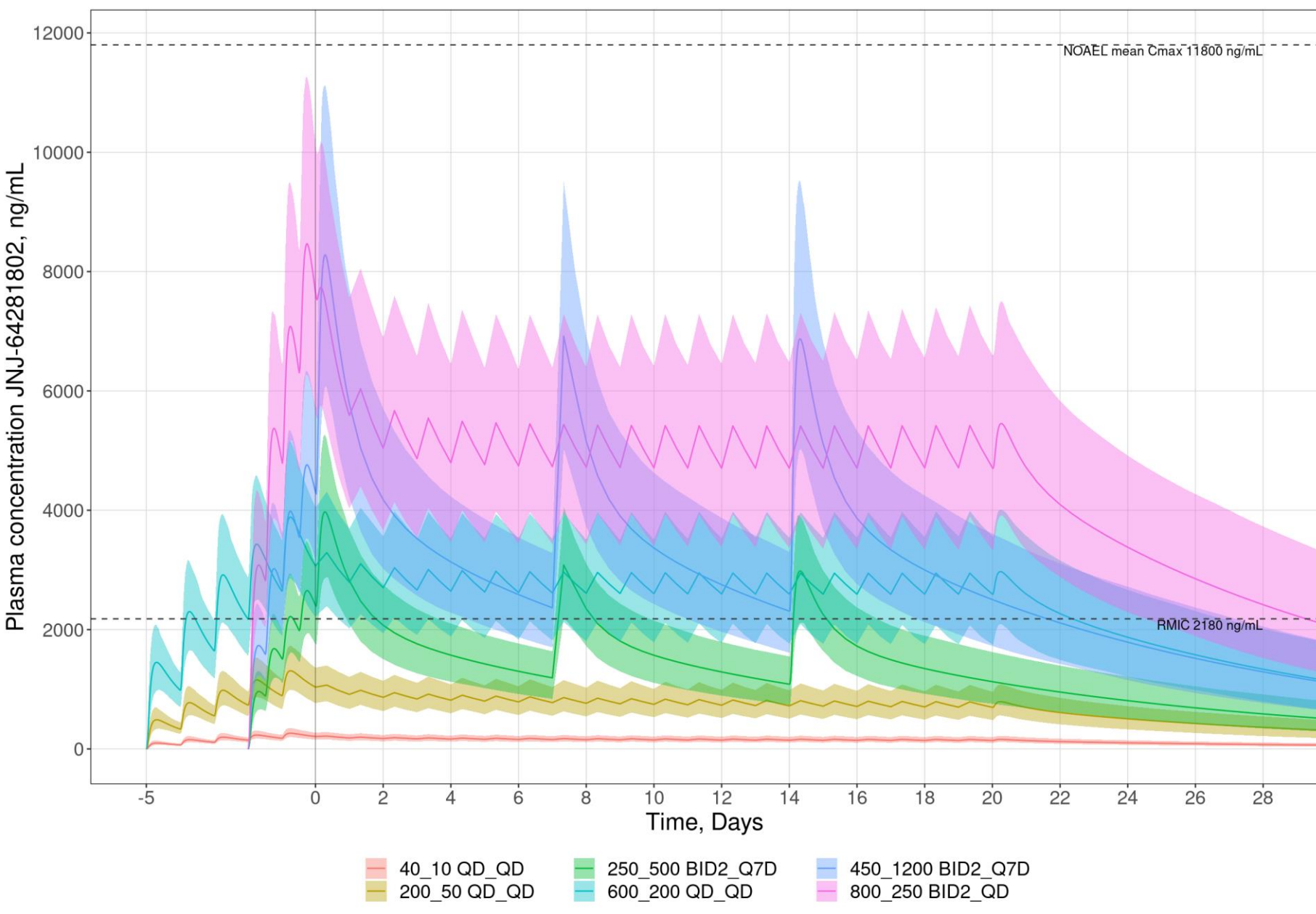
Figure 5. Estimates of effective reproductive number versus C_{avg,SS} for mosnodenvir in the CHIM study Cohort 1



PK-VKM based simulations were used to guide selection of one daily dose regimen and two weekly dose regimens for Cohort 2 (C2) with the aim to further characterize the PK/PD relationship of mosnodenvir (Figure 6, Tables 1-2):

- C2 daily: 800 mg BID for 2 days + 250 mg QD for 21 days**
- C2 weekly high: 450 mg BID for 2 days + 1200 mg Q7D on Study Day 1, 8, 15**
The two regimens were selected to maximize mosnodenvir antiviral activity (Table 2) within NOAEL safety limits (Table 1) for daily and weekly dosing, respectively.
- C2 weekly low: 250 mg BID for 2 days + 500 mg Q7D on Study Day 1, 8, 15**
Mosnodenvir antiviral activity was simulated between medium and high dose of Cohort 1 (Table 2).

Figure 6. Simulated mosnodenvir mean concentration profiles



PopPK model-based simulations. Solid lines: mean; shaded area: 95% percentile interval. C1 mosnodenvir in fasted conditions, C2 in fed conditions. Color legend: dose regimens presented as loading_maintenance in mg. Note: x-axis in time relative to Study Day 1 (inoculation).

Based on the mosnodenvir **PopPK model simulations**, Figure 6 shows that simulated:

- mean maintenance concentration **C2 daily** > **C1 high dose**
 - mean maintenance concentration **C2 weekly high** $\approx$ **C1 high dose** and > RMIC up to Study Day 21
 - mean maintenance concentration **C2 weekly low** is between **C1 medium dose** and **C1 high dose**;
- to be confirmed in Cohort 2 of the CHIM study.

Table 1. Simulated mosnodenvir mean C_{max} and AUC_{24h}

PK parameter	C2 daily	C2 weekly high	C2 weekly low	NOAEL safety threshold
Mean (SD)				
Study day	Day -1	Day 1	Day 1	NA
C _{max} (ng/mL)	8,580 (3,250)	8,460 (3,320)	4,050 (1,560)	11,800 (1,360)
AUC _{24h} (ng·h/mL)	171,000 (64,700)	166,000 (61,900)	81,100 (30,200)	177,000 (57,300)

PopPK model-based simulations. NOAEL, no adverse effect level.

Table 2. Simulated inhibition of DENV-3 RNA in the CHIM study

Median (95% percentile interval)	Placebo	C1 low dose	C1 medium dose	C1 high dose	C2 daily	C2 weekly high	C2 weekly low
# participants undetectable RNA up to D29	0 (0, 0)	0 (0, 1)	2 (0, 4)	4 (2, 6)	5 (3, 6)	5 (2, 6)	3 (1, 5)
AUC _{D1+D29} RNA (log10 copies *day/mL)	5.02 (4.76, 5.26)	4.80 (4.41, 5.08)	4.03 (1.94, 4.69)	1.50 (1.10, 3.72)	1.20 (1.07, 2.71)	1.34 (1.09, 3.24)	2.66 (1.29, 4.33)
Time to first detectable RNA (Study Day)	3.0 (3.0, 3.0)	3.0 (3.0, 4.5)	9.0 (4.0, 66)	NA (12, NA)	NA (47, NA)	NA (18, NA)	NA (6.0, NA)

PK-VKM-based simulations with N=6 participants per dosing arm. RNA denotes DENV-3 RNA.

Conclusions

- A semi-mechanistic **exposure-response VKM** adequately described observed DENV-3 RNA profiles under placebo and different mosnodenvir dose regimens in the first cohort of a Phase 2a CHIM study.
- The PK-VKM **informed** estimation of the mosnodenvir **prophylactic drug effect** in Cohort 1 and **dose selection** for Cohort 2 using model-based simulations. The model has yet to be evaluated on observed Cohort 2 data.
- The CHIM does not reflect **field conditions** and mosnodenvir is further tested in a Phase 2 study in endemic regions.

References

- WHO dengue fact sheet: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>
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