

Clinical Update on the Integrase Inhibitor GS-9137

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HIV Lifecycle And Existing Drug Targets

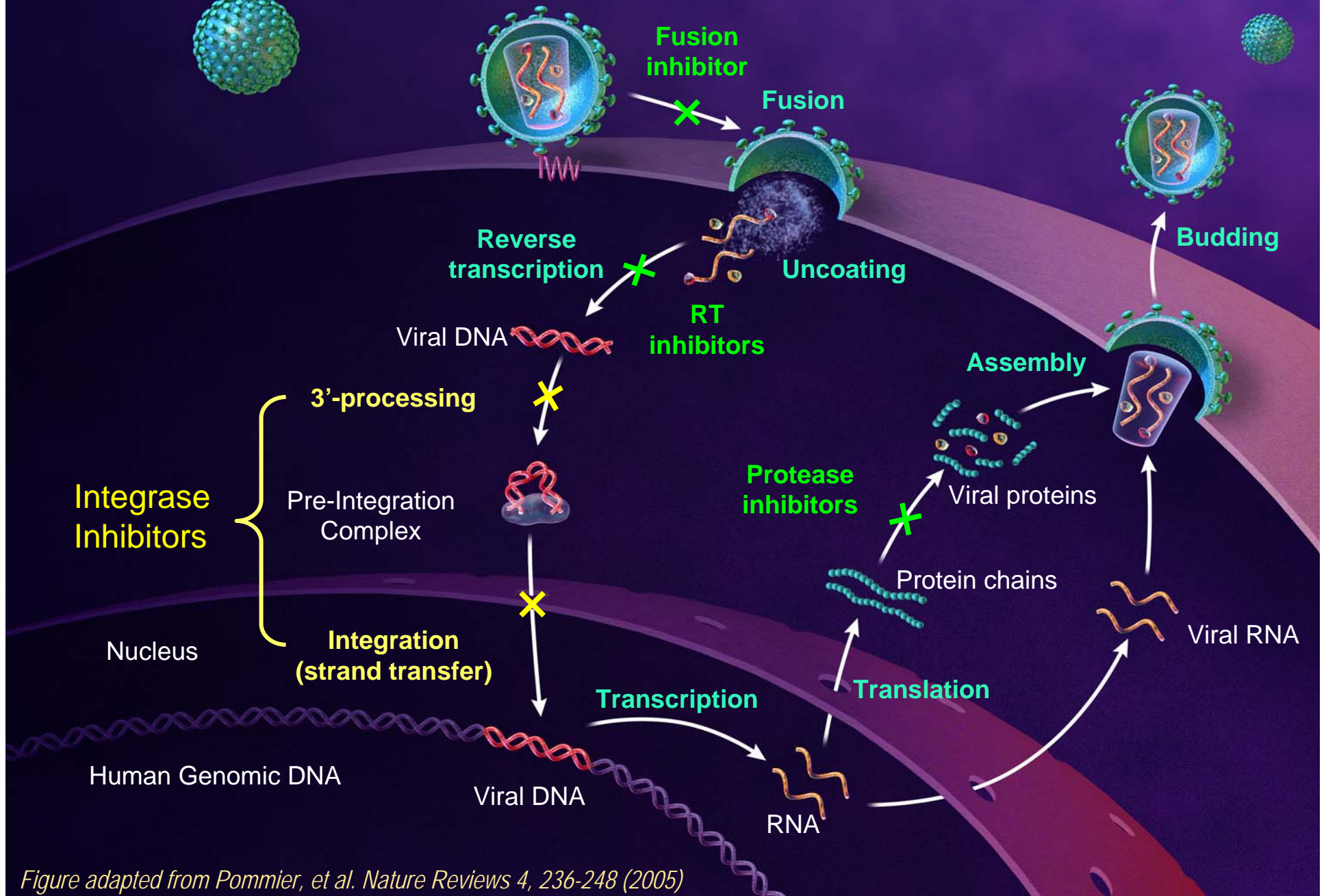
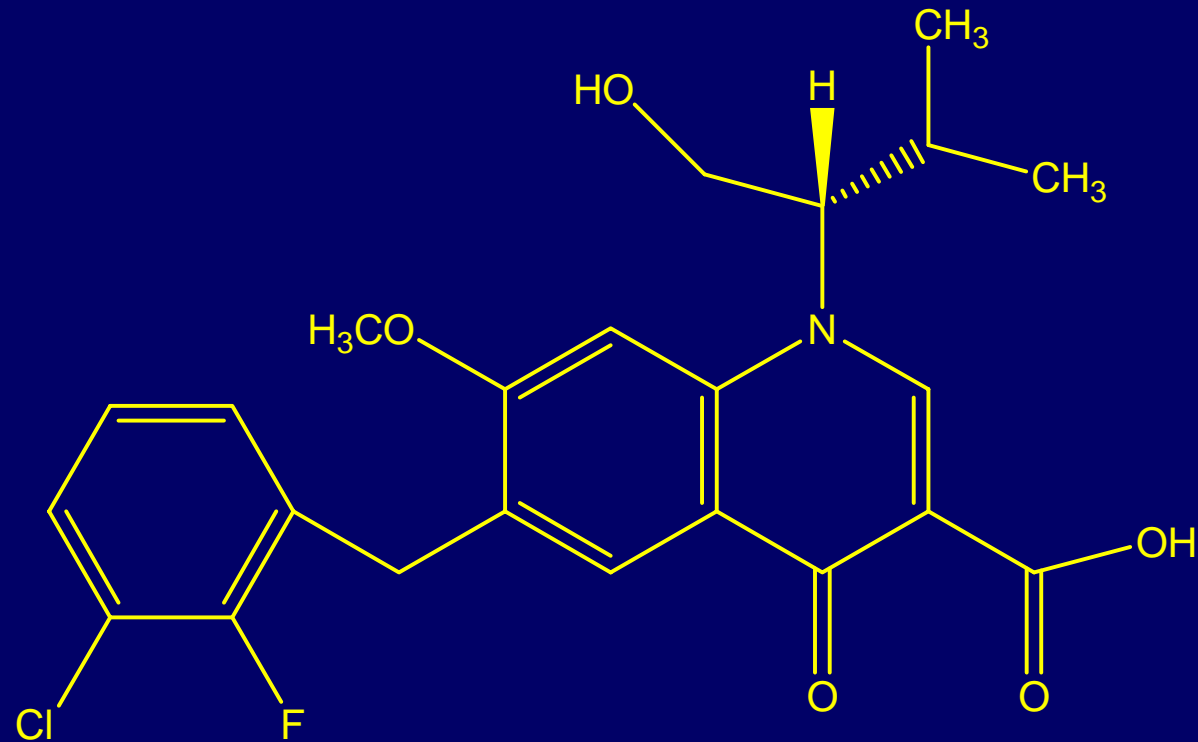


Figure adapted from Pommier, et al. Nature Reviews 4, 236-248 (2005)

GS-9137/JTK-303 Background



- Dihydroquinoline carboxylic acid
- Strand transfer inhibitor of HIV integrase

GS-9137 Background

- **Potent anti-HIV activity in vitro**
 - Serum-free IC₅₀ of 0.2 nM against HIV-1
 - Protein binding-adjusted IC₅₀ in human PBMCs of 16 nM
- **GS-9137 has NO effect on:**
 - HIV-1 reverse transcriptase
 - HIV-1 protease
 - Human topoisomerases I & II
 - Seven enzymes tested at 10μM
 - (PLA₂, Cox1, NOS, PDE-IV, PKC, AChE, MAO)

GS-9137 Background

- **Rat and dog chronic toxicology studies**
 - Maximum doses of 2000 mg/kg/d and 100 mg/kg/d
 - No evidence of dose-limiting toxicities

- **No reproductive toxicity**

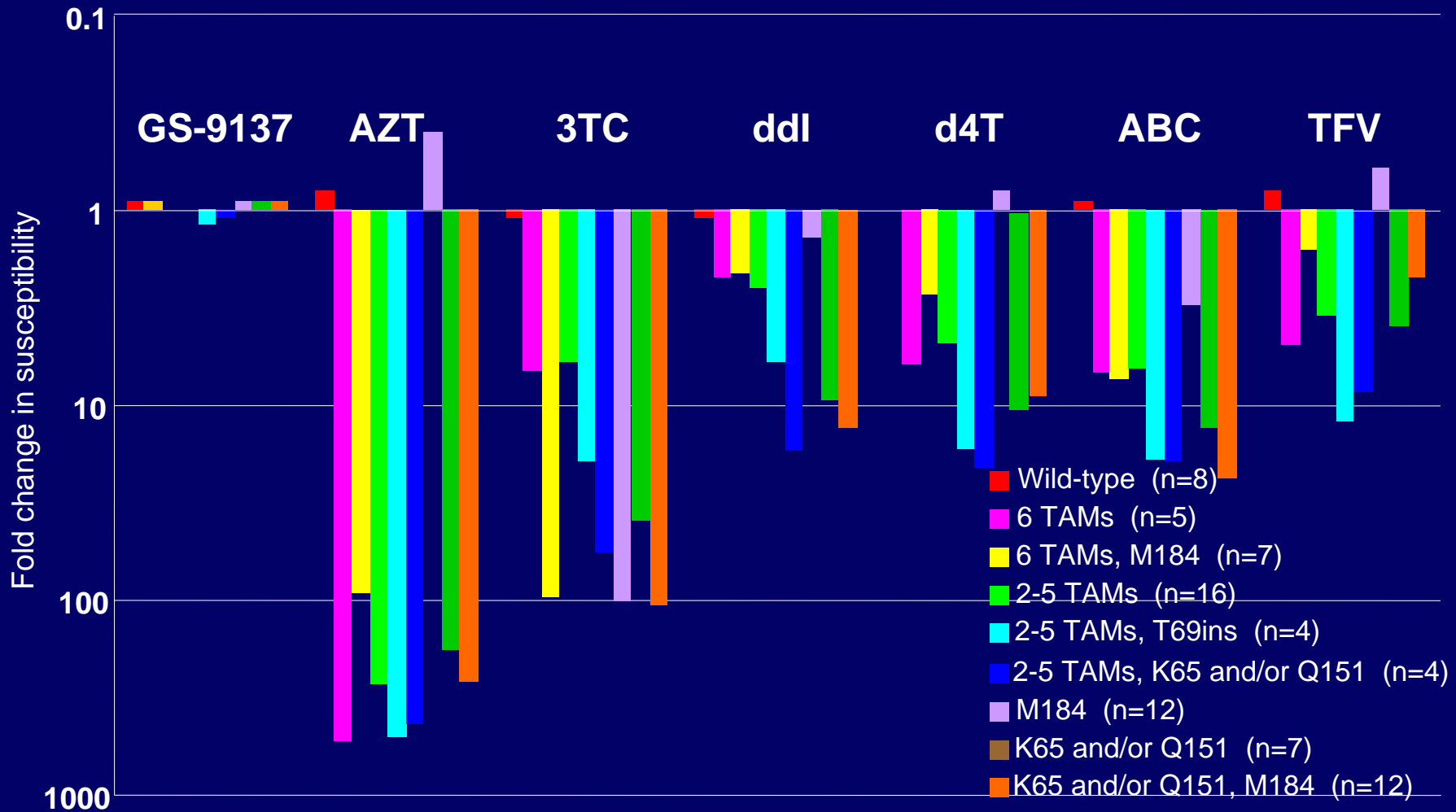
- **No immunotoxicity**

- **No genotoxicity**

- **At least 2- to 3-fold safety margins at highest human dose**

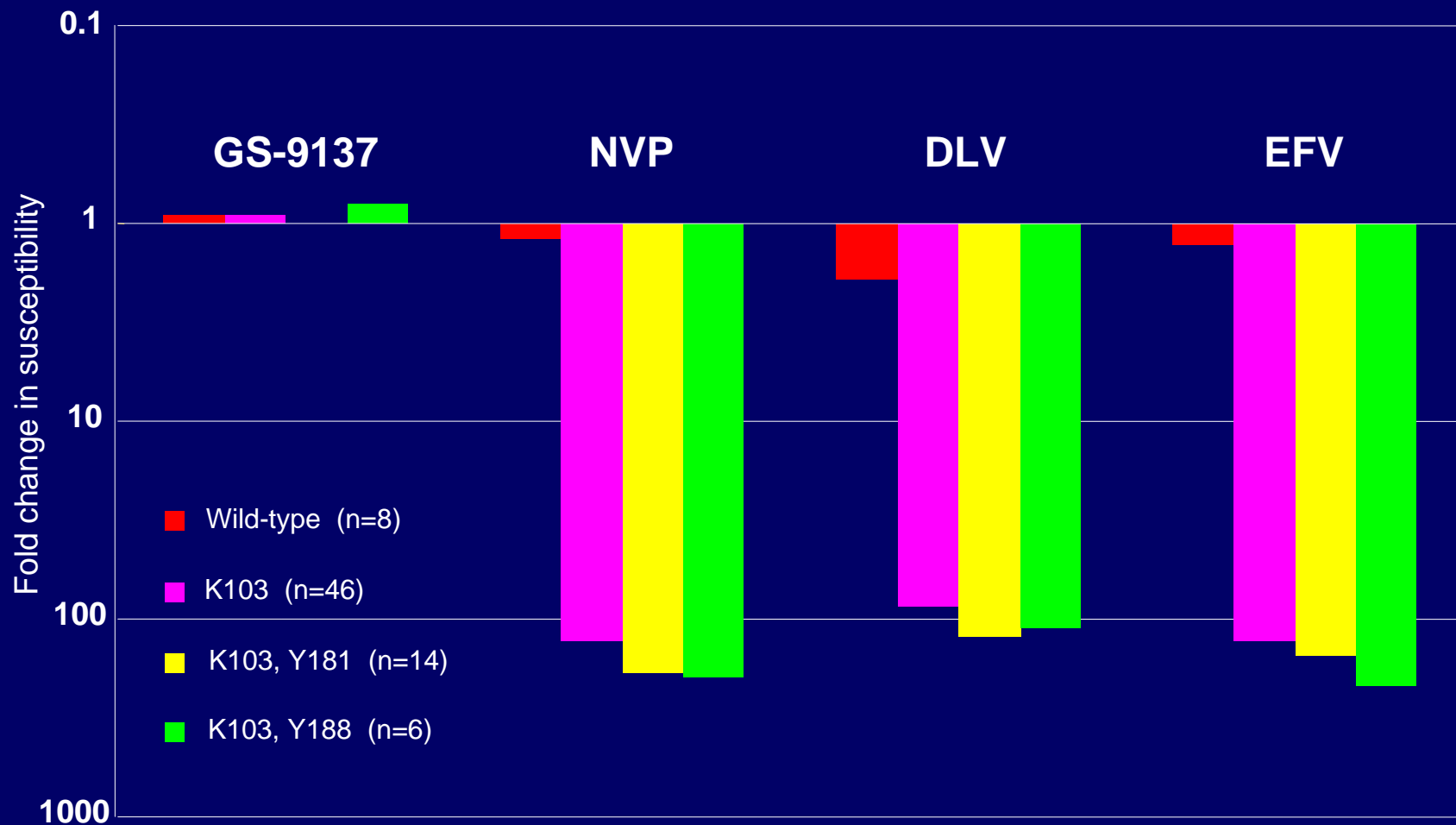
GS-9137 Is Active Against NRTI-Resistant Viruses

(PhenoSense™ Assay, Monogram Biosciences)



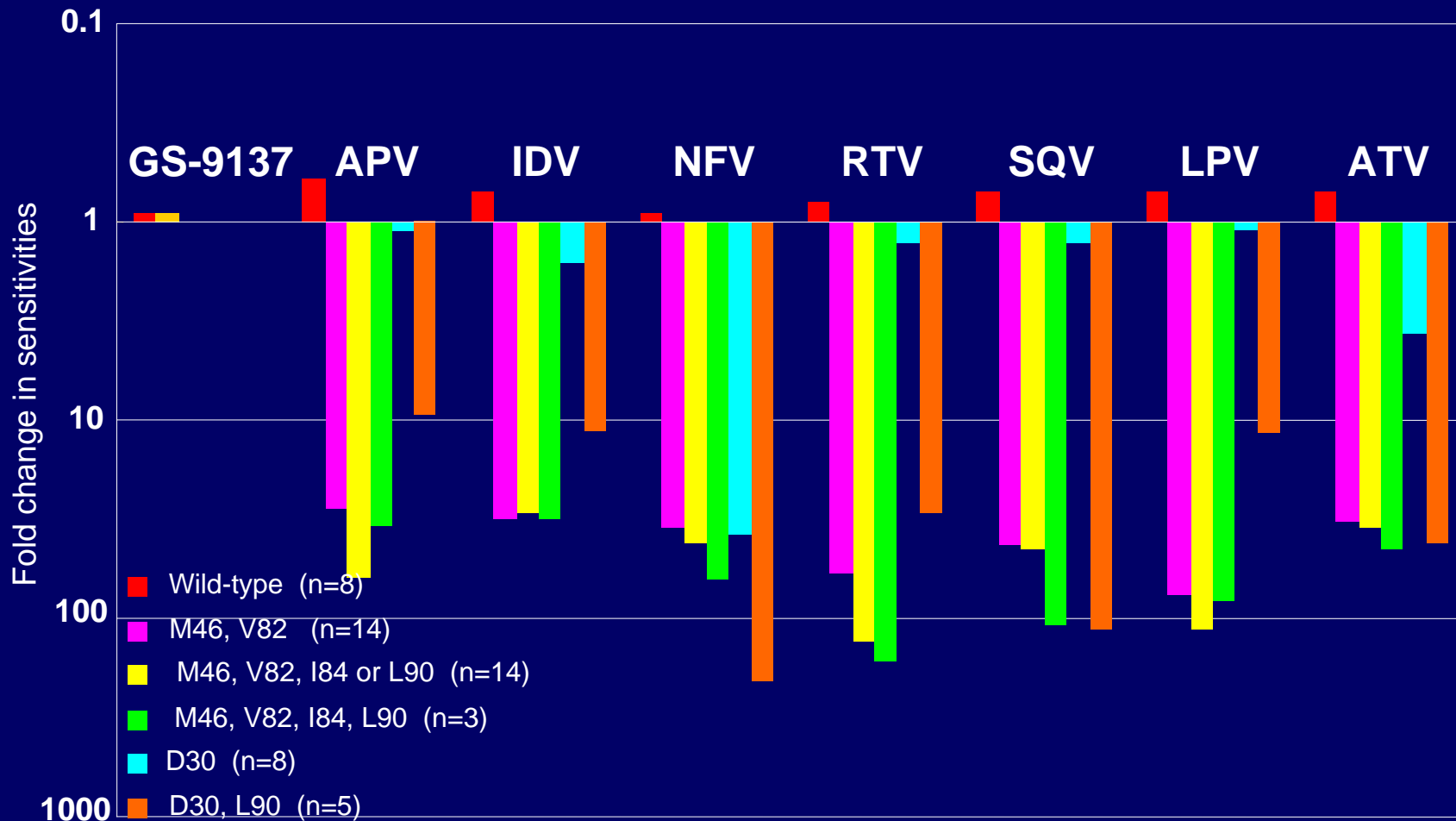
Japan Tobacco, unpublished data

GS-9137 Is Active Against NNRTI-Resistant Viruses (PhenoSense™ Assay, Monogram Biosciences)



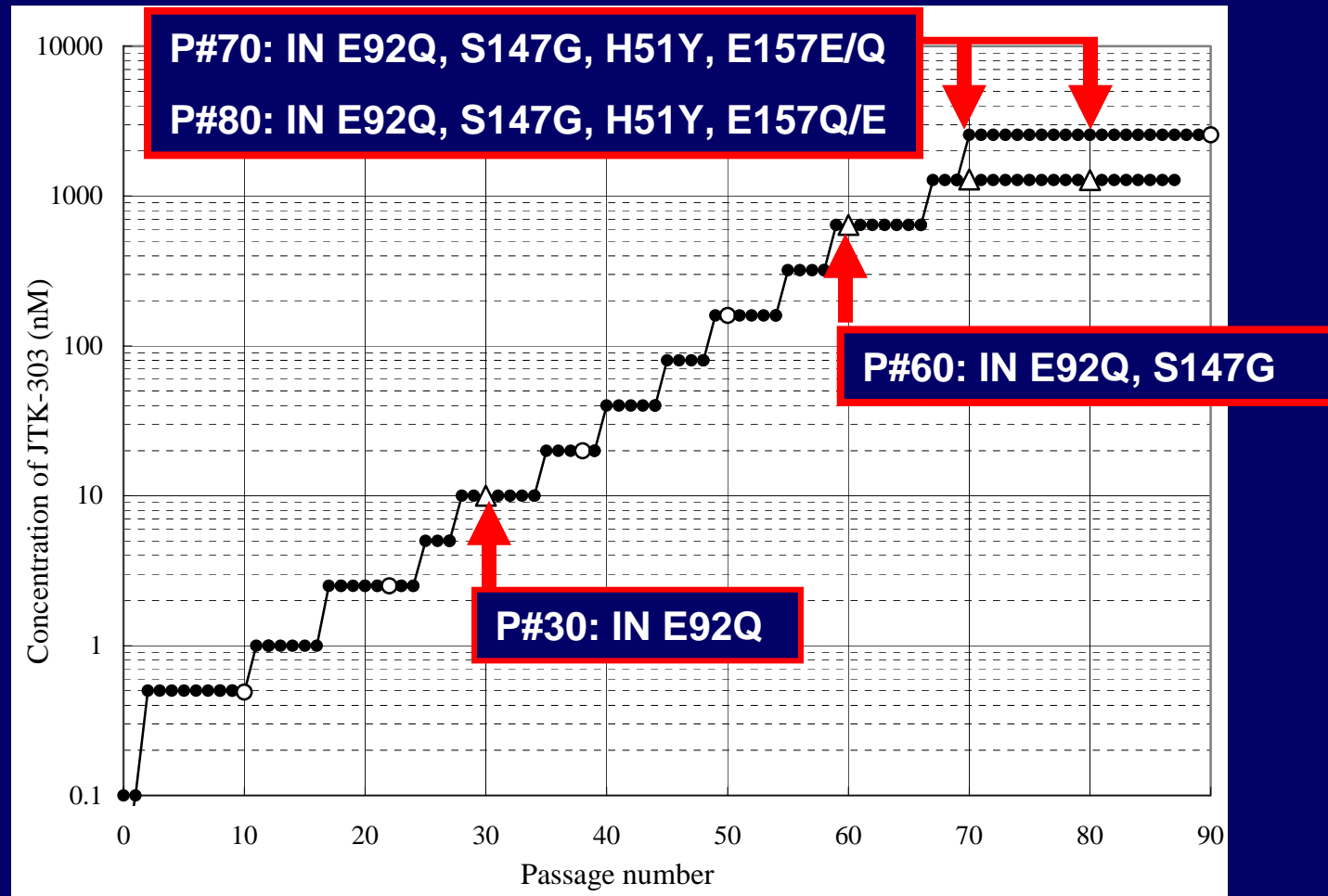
Japan Tobacco, unpublished data

GS-9137 Is Active Against PI-Resistant Viruses (PhenoSense™ Assay, Monogram Biosciences)



Japan Tobacco, unpublished data

In Vitro Resistance Selections Of HIV-1 IIB With GS-9137 (Japan Tobacco)



GS-9137 Pharmacokinetics

- **Preclinical pharmacokinetics**
 - Metabolism: oxidative (CYP3A) and glucuronidation pathways
 - Moderate inducer of CYP3A, not an inhibitor
- **Pharmacokinetics of GS-9137**
 - Single dose PK in healthy volunteers: GS-9137 exhibited generally dose-proportional pharmacokinetics
 - Higher relative systemic exposure when dosed with food
 - Half-life ~ 3 hours

Pharmacokinetics of Ritonavir-boosted GS-9137

- **Ritonavir**
 - Potent inhibitor of CYP3A4
 - Often used to “boost” exposure of protease inhibitors to maintain therapeutic trough (C_{\min}) concentrations
- **Pharmacokinetics of ritonavir-boosted GS-9137**
 - 20-fold improvement in systemic exposure (AUC) and high trough (C_{τ}) concentrations
 - Long plasma half-life (~9 hours)

GS-US-183-0101

Proof of Concept Study Design

Randomized, double blind, placebo-controlled 10 day monotherapy study

Screening	Randomization	Dosing/PK	Follow up
Inclusion	Cohort (Sequential) #	Day 1-10	Day 11-21
HIV +, HBV -, HCV-	200mg BID 6 Placebo BID 2	Treatment: GS-9137 or Placebo	Off treatment
Naïve, Experienced Off ARV	400mg BID 6 Placebo BID 2	PK: Serial trough sampling	PK: Serial trough sampling
HIV-RNA: 10,000-300,000	800mg BID 6 Placebo BID 2	Intensive PK Day 1 and 10	
CD4+: >200 cells	800mg QD 6 Placebo QD 2		
	50mg/100r QD 6 Placebo/100r QD 2		

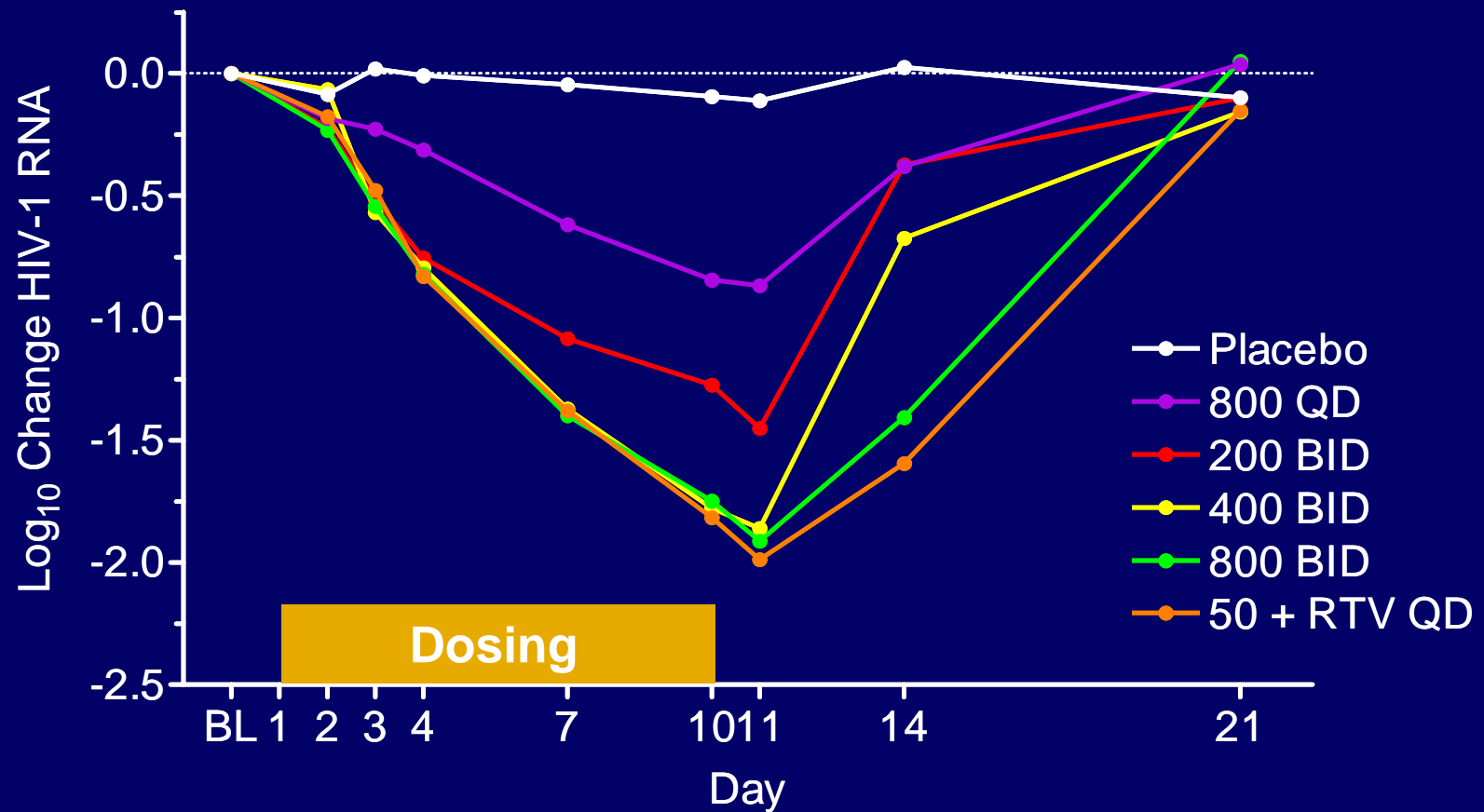
Study endpoints: Changes in HIV RNA, safety and tolerability, PK and PD

Demographics and Baseline Characteristics

N	40
Mean Age	39
Male / Female	39 / 1
White / Black	36 / 4
Treatment naïve	15 (11 / 4)
Treatment experienced	25 (19 / 6)
N (active drug/placebo)	
Mean HIV-1 RNA	4.75
Log₁₀ copies/mL (min, max)	(3.69, 5.73)
HIV RNA > 100,000	30%
Mean CD4⁺ (cells/mm³)	442

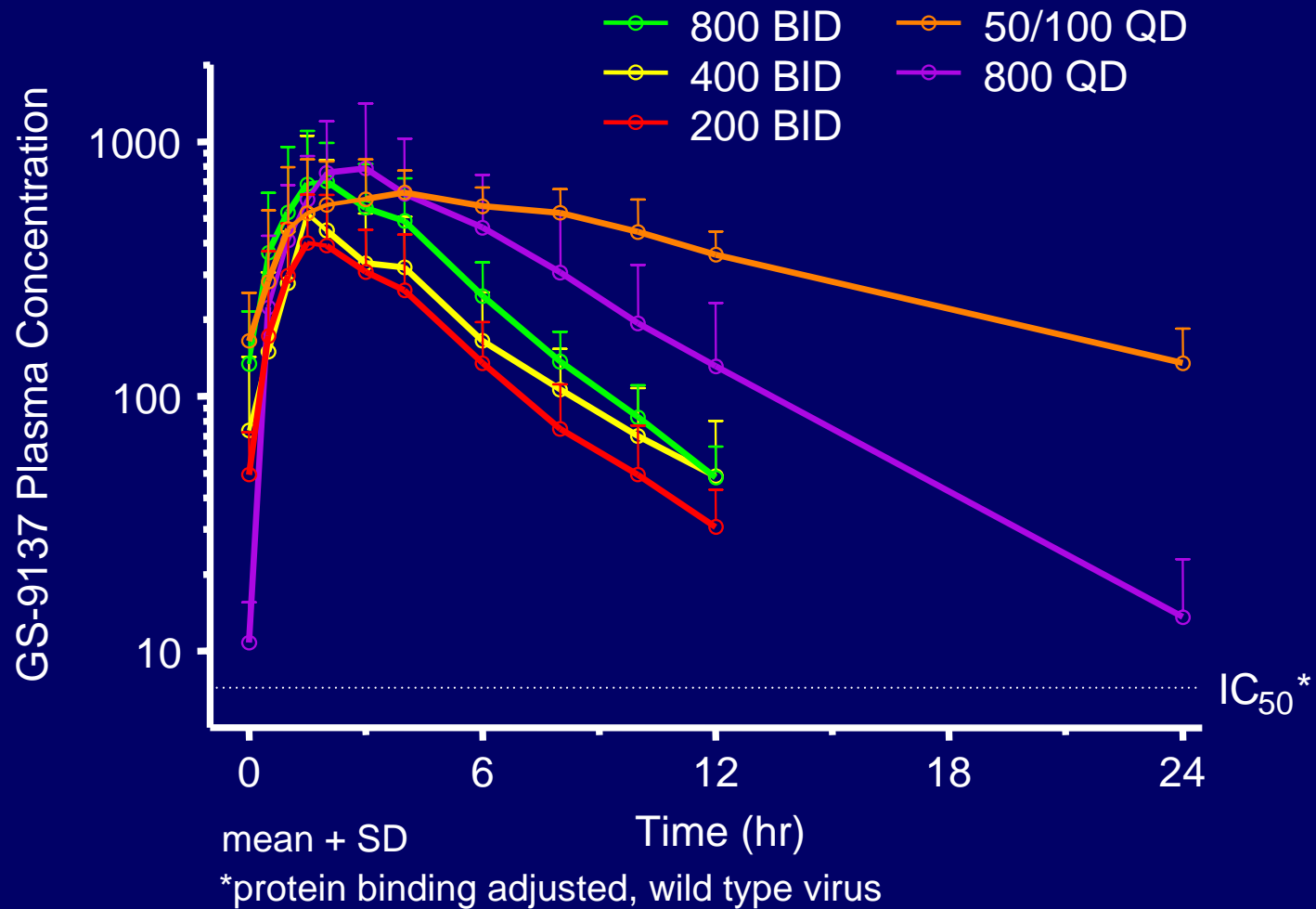
GS-9137

Mean Change in HIV-1 RNA

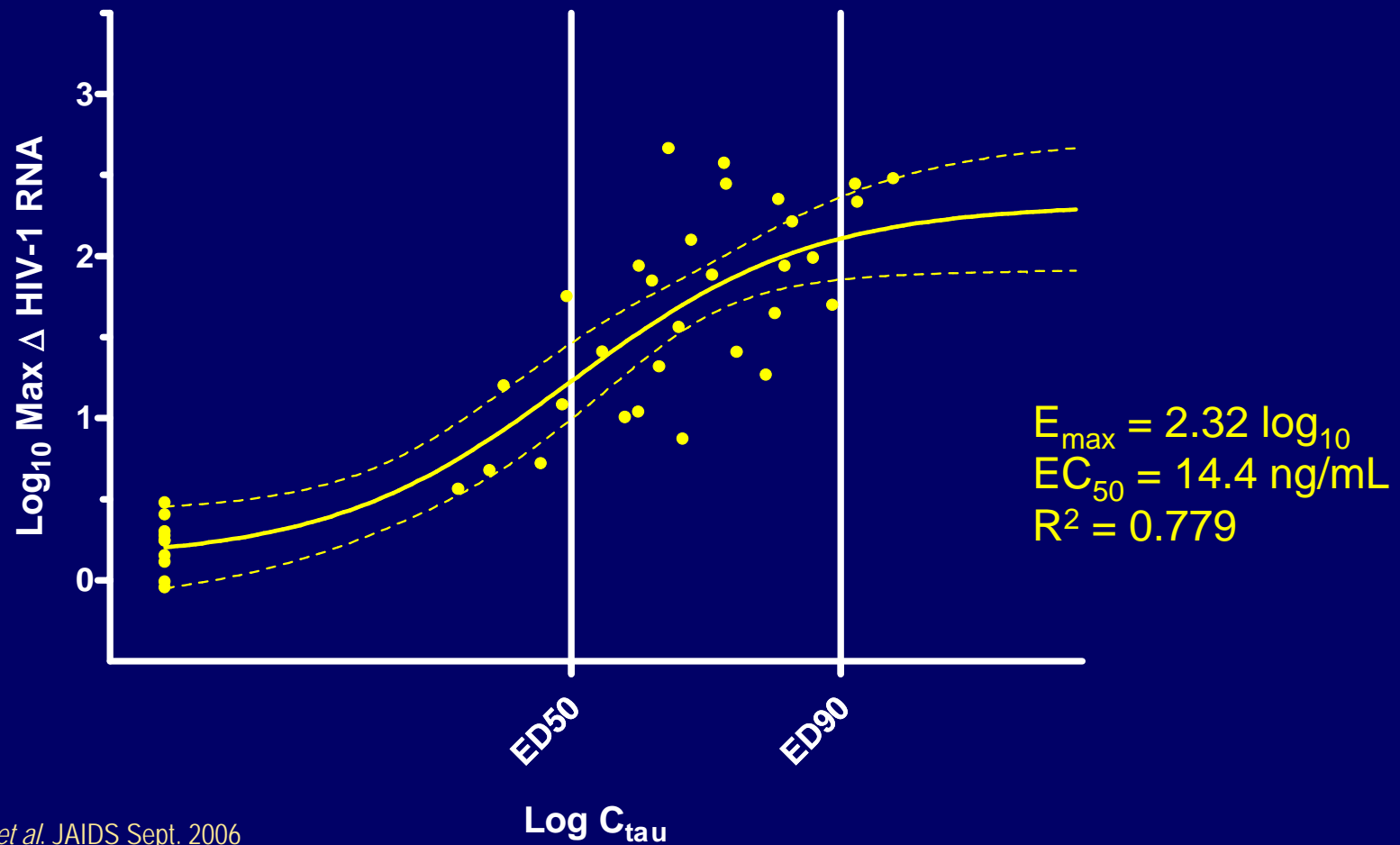


GS-9137

Steady-State Pharmacokinetics



GS-9137 Pharmacologic (Emax) Model



Genotyping Analyses

- **RT, PR and IN genotypes generated at Baseline, Day 11, Day 21 (all patients)**
- **At Baseline:**
 - 12 patients had evidence of primary resistance
 - NRTI (n=2), NNRTI (n=7), and PI (n=3)
 - K103N (EFV-R) was the most frequent BL mutation
- **By Day 11 and Day 21:**
 - No patients developed INI-R mutations
 - No patients developed mutations selected by RTV

Safety

- **All patients completed study, no study drug discontinuations**
- **No serious adverse events**
- **GS-9137/(r) was well tolerated with adverse events and graded laboratory abnormalities similar to placebo**
 - **Drug-related adverse events generally mild and resolved on treatment**
 - **No evidence of dose-related toxicities**

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