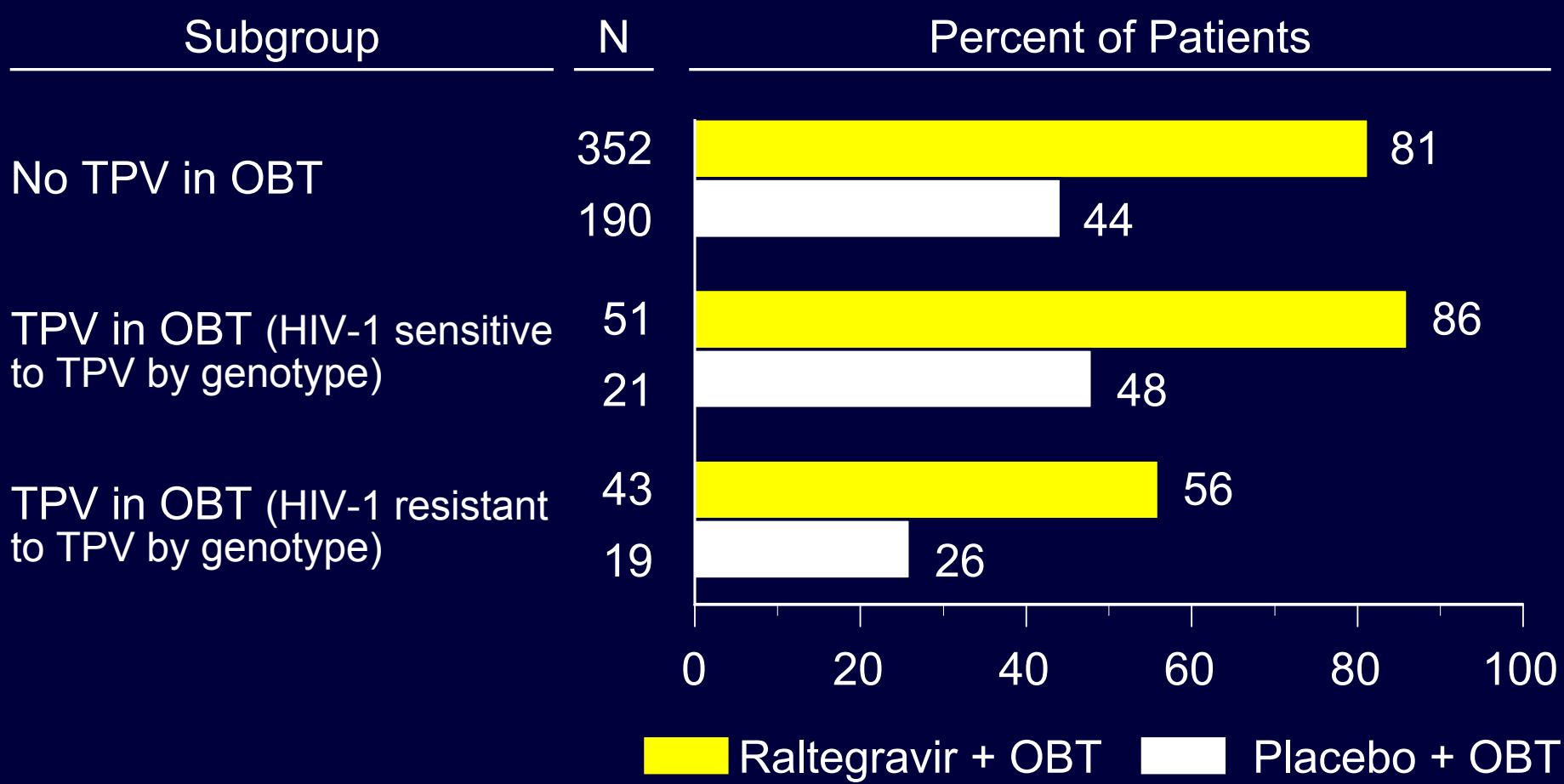
Background Incidence of Neoplasms Comparison With Published Literature

	Raltegravir N=758 820 PY		Published Studies	Number of Papers Reviewed (n=22)
	n	Incidence Rate†	Rate Range†	
Patients with neoplasm	19	2.3	0.73 - 4.8	5
Kaposi's sarcoma	4	0.5	0.12 - 4.5	15
Non-Hodgkin's lymphoma	3	0.4	0.11 - 1.6	15
SC carcinoma - anogenital	5	0.6	0.01 - 0.15	9
SC carcinoma - other‡	1	0.1	0.02 - 0.04	6
Rectal cancer	1	0.1	0.01 - 0.23	7
Hepatocellular carcinoma	1	0.1	0.01 - 0.22	10
Non-melanoma skin cancer	5	0.6	0.01 - 0.36	7

PY = patient-years of exposure.
† Events per 100 patient-years.
‡ Other includes mouth/lip/tonsil/larynx/pharynx for published studies and vocal cord for raltegravir.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Protocols 018 and 019 Combined Efficacy† Percent of Patients With HIV RNA <400 copies/mL at Week 16 by Tipranavir (TPV) Use in OBT (Original Filing)



† Virological failures carried forward.

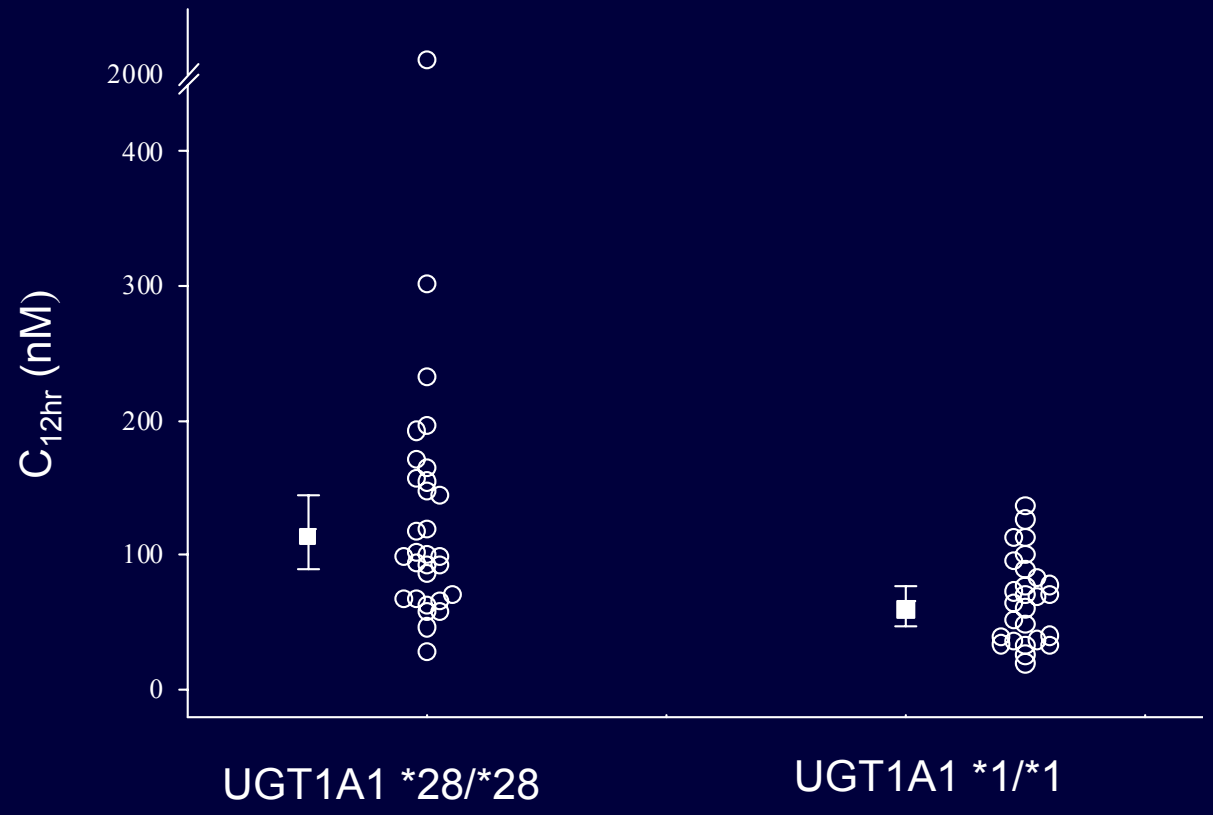
Treatment-Emergent Mutations in Virologic Failures From Treatment-Naïve Study P004

Treatment Group	RAL	3TC	TFV	EFV
RAL 100	V151I N155H D232D/N G163R/G	M184M/I/V K65K/R	K65K/R	---
RAL 200	---	M184M/I/V	---	---
	---	---	---	---
	N155H	M184M/I/V	---	---
	---	M184V	---	---
EFV	S230S/N*	K65R	K65R	G190E

* S230S/N is a common polymorphism not thought to affect sensitivity to integrase inhibitors.
All other mutations were associated with reduced drug sensitivity. (--- indicates no mutations).

UGT1A1 Polymorphism Study†

Individual values for raltegravir $C_{12\,hr}$ following administration of single oral doses of 400-mg raltegravir to healthy subjects with UGT1A1*28/*28 (N=30) or with UGT1A1*1/*1 (N=27)

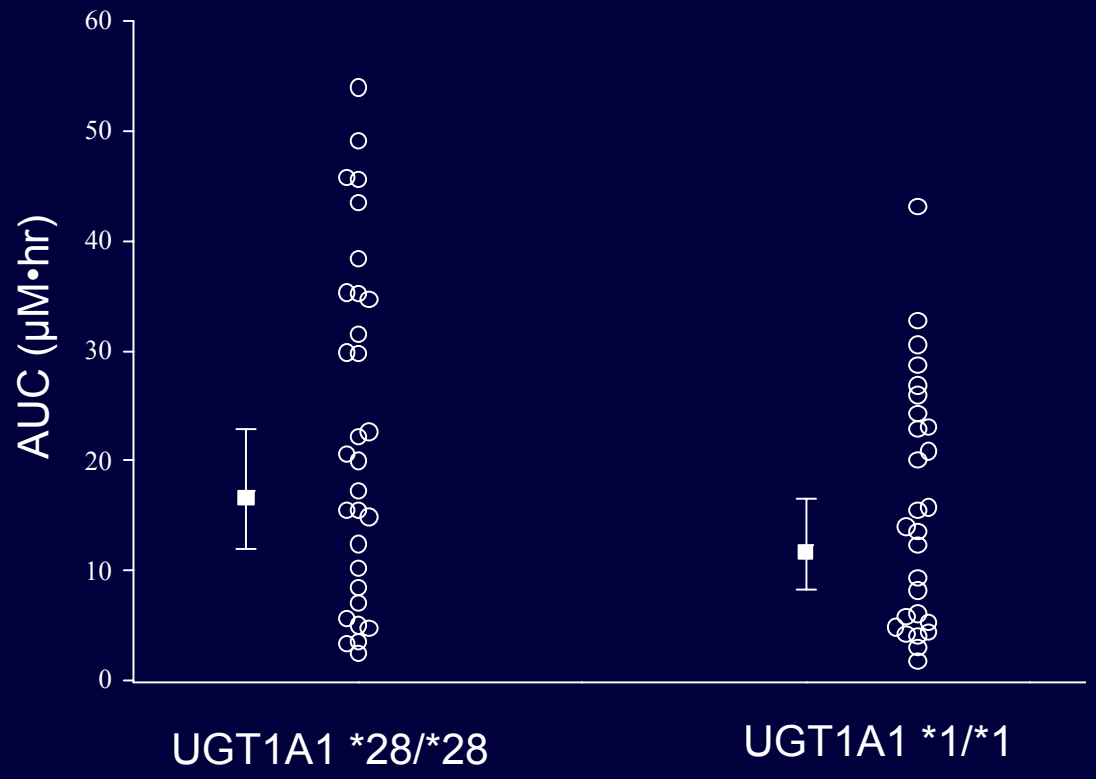


Open Circle = Individual Value
Closed Square = Geometric Mean
Error Bars = 95% Confidence Interval

† Data submitted and under review by FDA.

UGT1A1 Polymorphism Study†

Individual values for raltegravir $AUC_{0-\infty}$ following administration of single oral doses of 400-mg raltegravir to healthy subjects with UGT1A1*28/*28 (N=30) or with UGT1A1*1/*1 (N=27)



Open Circle = Individual Value
Closed Square = Geometric Mean
Error Bars = 95% Confidence Interval

† Data submitted and under review by FDA.

Herpes Zoster
400 mg BID Double-Blind Cohort
(Protocols 005, 018, 019)

- Proportion of patients with herpes zoster infection reported as clinical adverse experiences
  - 3.4% (17/507) for the raltegravir group
  - 0.7% (2/282) for the placebo group
- Crude exposure adjusted rates
  - Raltegravir 6.5 cases per 100 patient-years
  - Placebo 1.6 cases per 100 patient-years
- In patients in the raltegravir group
  - All the adverse experiences were reported as mild to moderate
  - 2 were considered drug-related
  - None were reported as serious
  - None lead to discontinuation

Distribution of Patients by Category of Percent Compliance (Protocols 018 and 019-Original Filing)

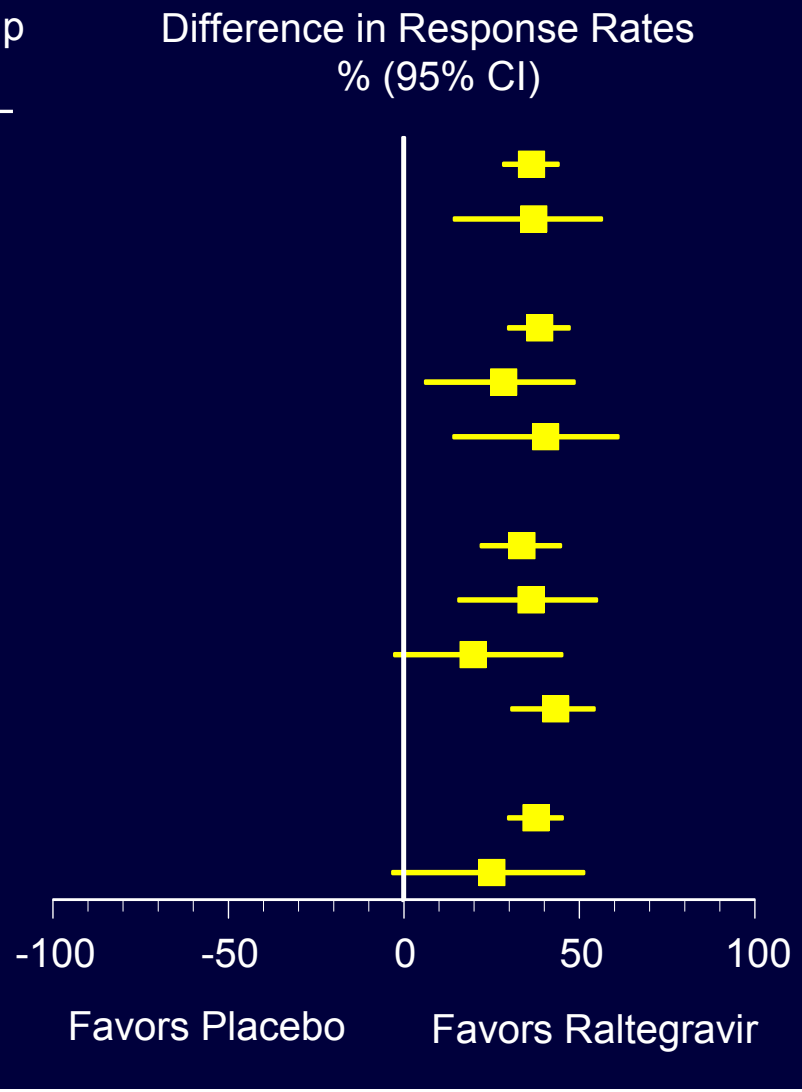
	Protocol 018‡		Protocol 019‡	
	Raltegravir N=232	Placebo N=118	Raltegravir N=230	Placebo N=119
Percent compliance†				
100%	193	102	184	89
90 to 99%	36	11	41	28
80 to 89%	0	2	2	2
70 to 79%	0	3	2	0
<70%	3	0	1	0

† Percent compliance is defined as [number of days on study drug/of days that the patient should have been on study drug] x 100.
‡ Plus OBT.

Protocols 018 and 019 Combined Efficacy Patients With HIV RNA <400 copies/mL at Week 16 by Subgroups (Original Filing)

Response Rates

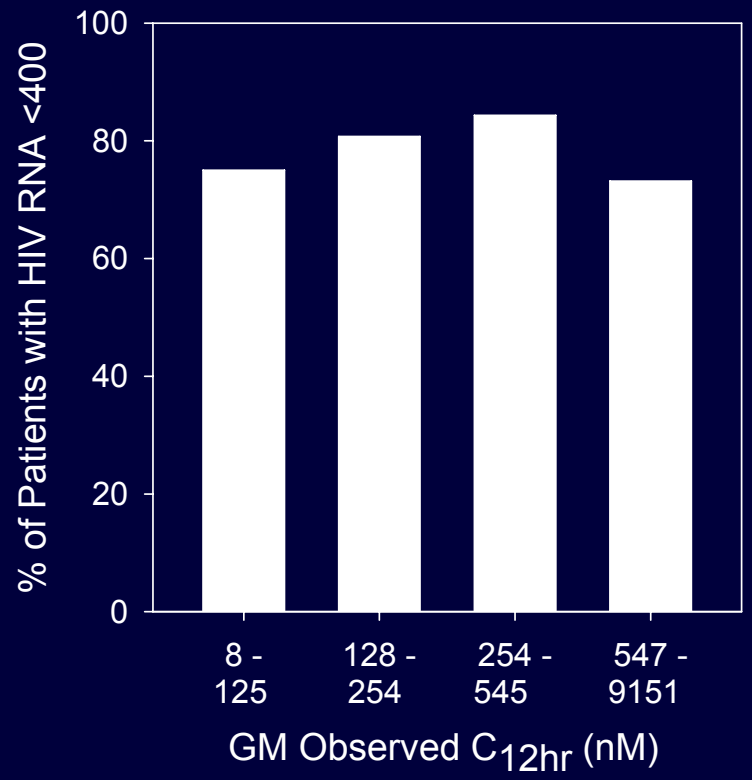
	Raltegravir Group n/N (%)	Placebo Group n/N (%)
Male	315/393 (80.2)	89/203 (43.8)
Female	40/54 (74.1)	10/27 (37.0)
White	238/292 (81.5)	71/166 (42.8)
Black	46/65 (70.8)	11/26 (42.3)
Hispanic	36/50 (72.0)	6/19 (31.6)
North America	148/185 (80.0)	45/97 (46.4)
South America	48/59 (81.4)	14/31 (45.2)
Asia/Pacific	32/37 (86.5)	12/18 (66.7)
Europe	127/166 (76.5)	28/84 (33.3)
Clade B virus	320/401 (79.8)	89/211 (42.2)
non-Clade B virus	28/39 (71.8)	7/15 (46.7)



Quartile Analysis of Potential Relationship Between C_{12hr} and HIV RNA<400

Pooled Data in Treatment-Experienced Patients (P005, P018, and P019)

- A similar percentage of patients had HIV RNA <400 at treatment week 16 in each quartile of observed raltegravir C_{12hr} values



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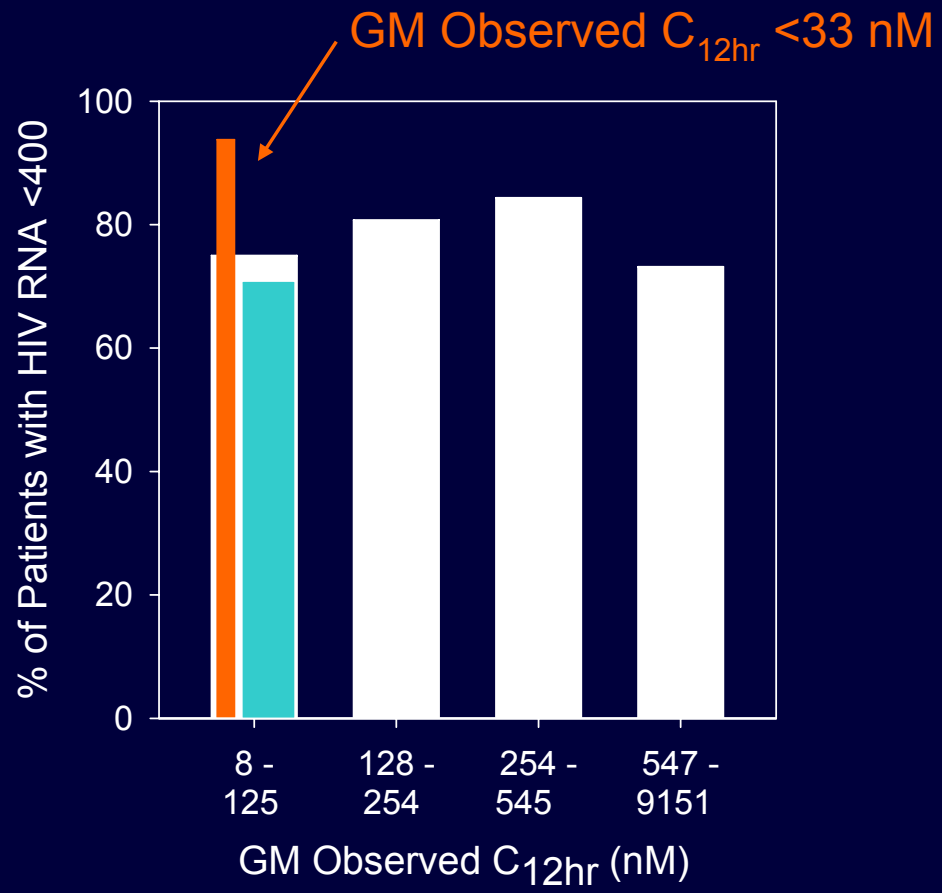
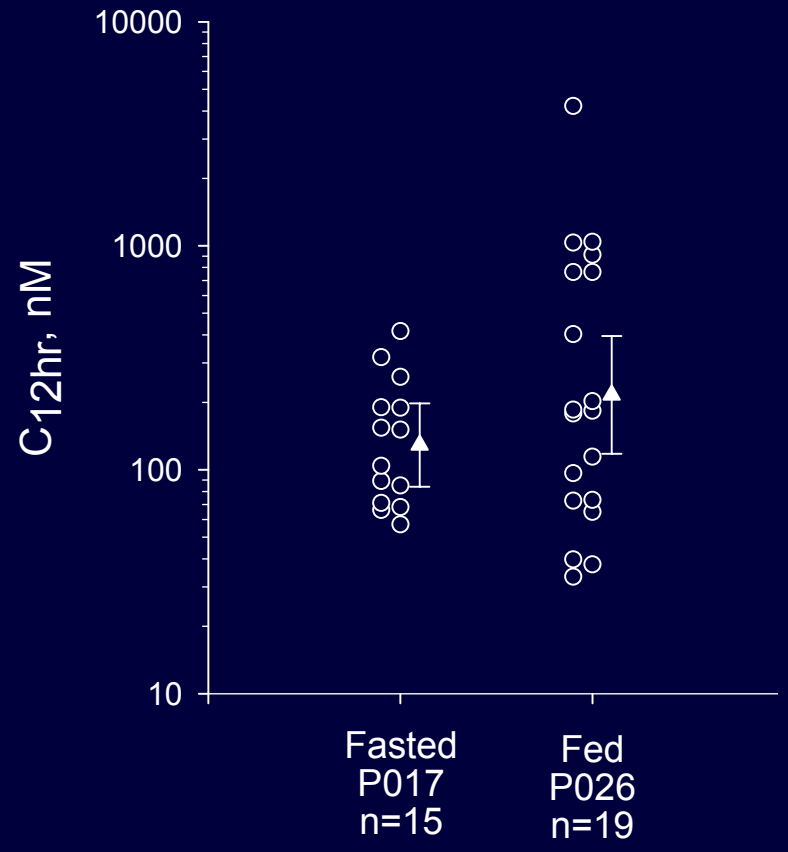
PK/PD for Low Outlier Patients



- 16 out of 332 patients had GM observed C_{12hr} values <33 nM (~in vitro IC_{95})
- These patients had a similar rate of treatment success compared to patients with other GM observed C_{12hr} values

Effect of a Moderate-Fat Meal

Cross-study comparison of the distribution of individual $C_{12\ hr}$ on day 4 of multiple, twice daily dosing of 400 mg in the fasted state or co-administered with a standardized moderate-fat meal

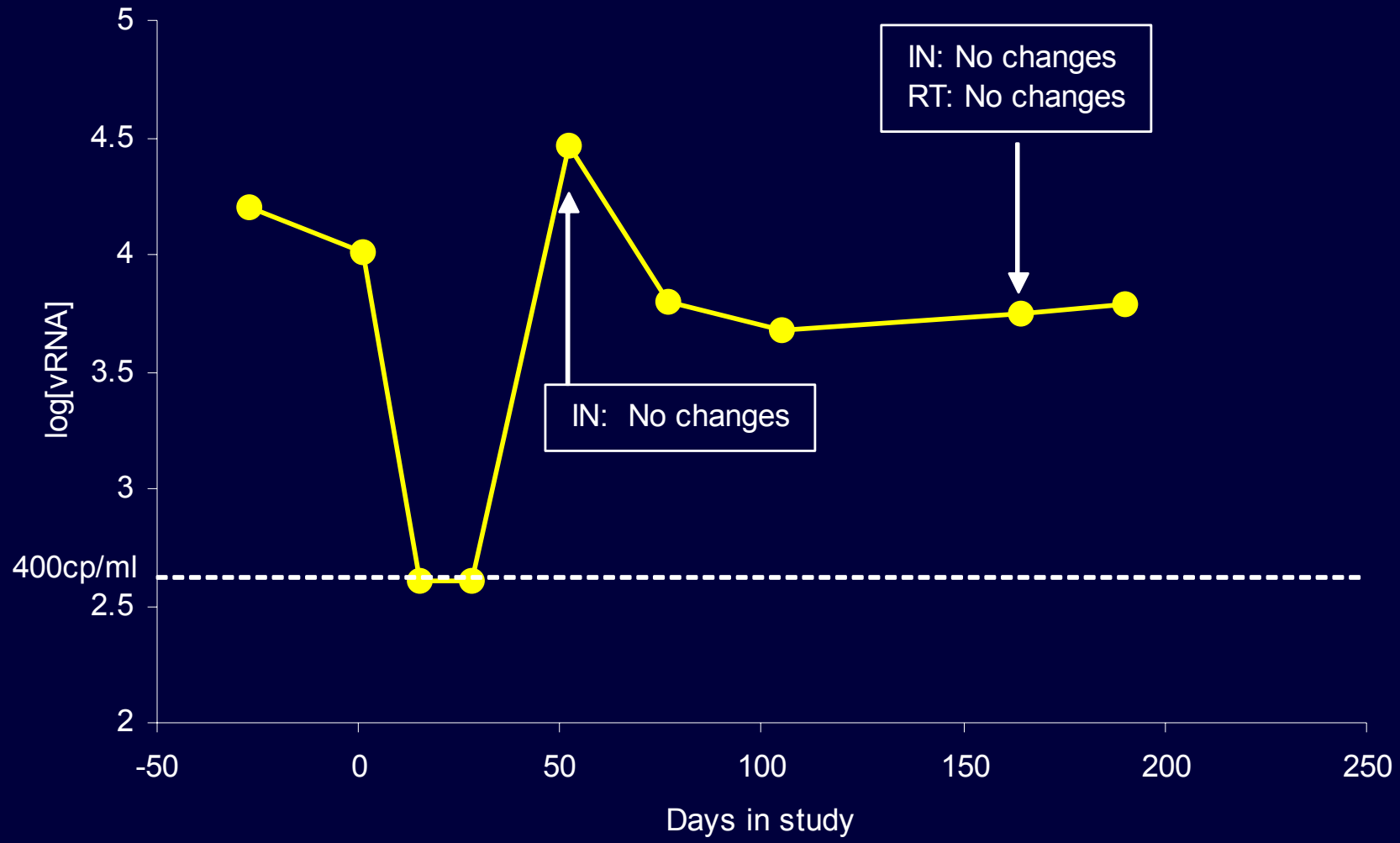


Open circles = individual values
Closed triangles = geometric mean
Error bars = 95% CI

Resistance Mutations in Protocol 018: Virologic Relapse Versus Non-response

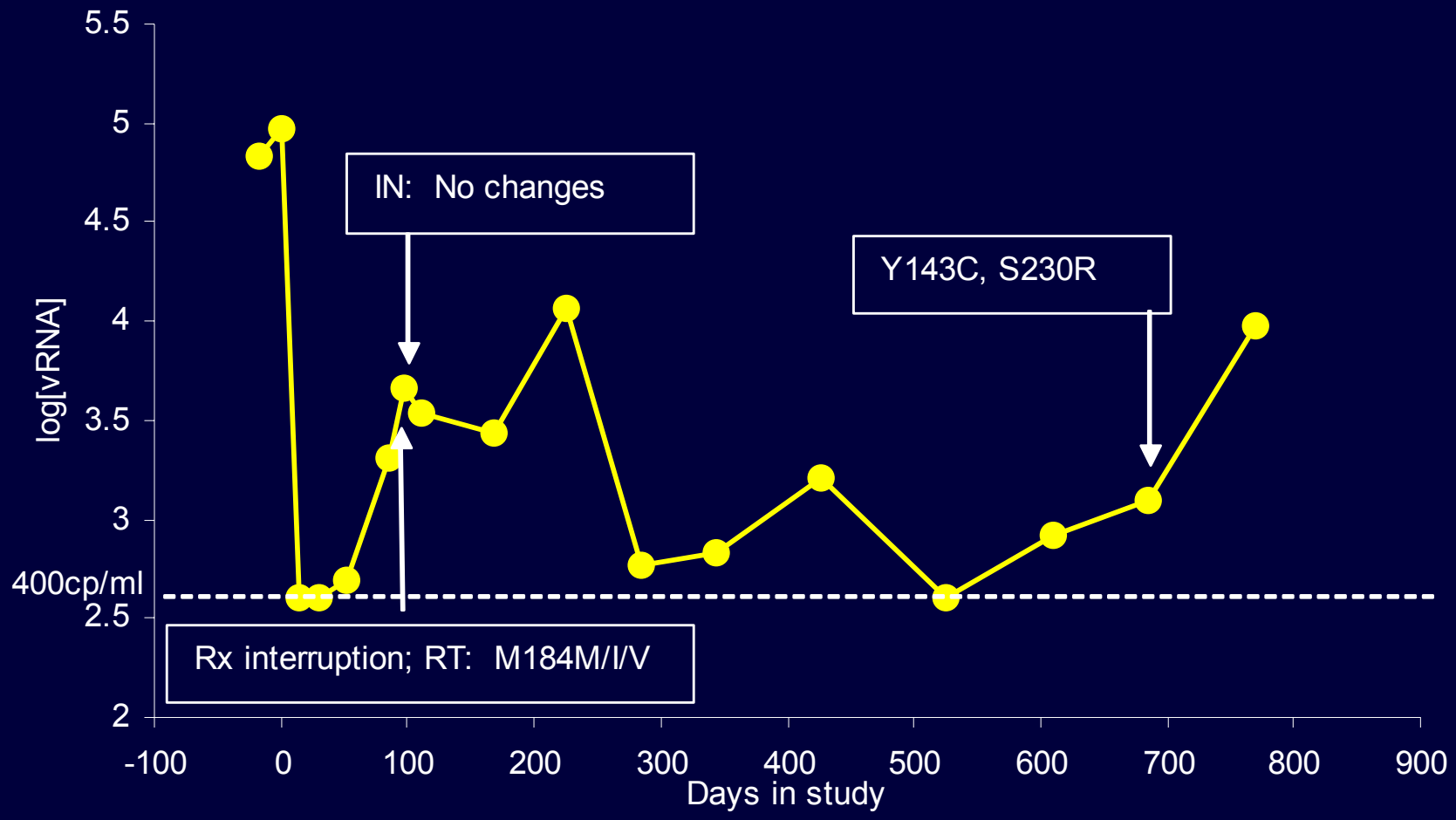
- Of 20 genotyped raltegravir virologic failures, only 1 was a non-responder
- Patient developed resistance to raltegravir (Y143H/R/YC at 4 weeks; Y143R/C, T97A, S230S/R at 18 weeks)
- Overall susceptibility score for OBT = 0
  - Patient's baseline virus was resistant to all components of OBT (SQV/r^R, FOS/r^R, TFV^R, FTC^R)

A Protocol 004 VF With No RT or IN Resistance Mutations*



* Data not reviewed by FDA. cp/ml = copies per mL.

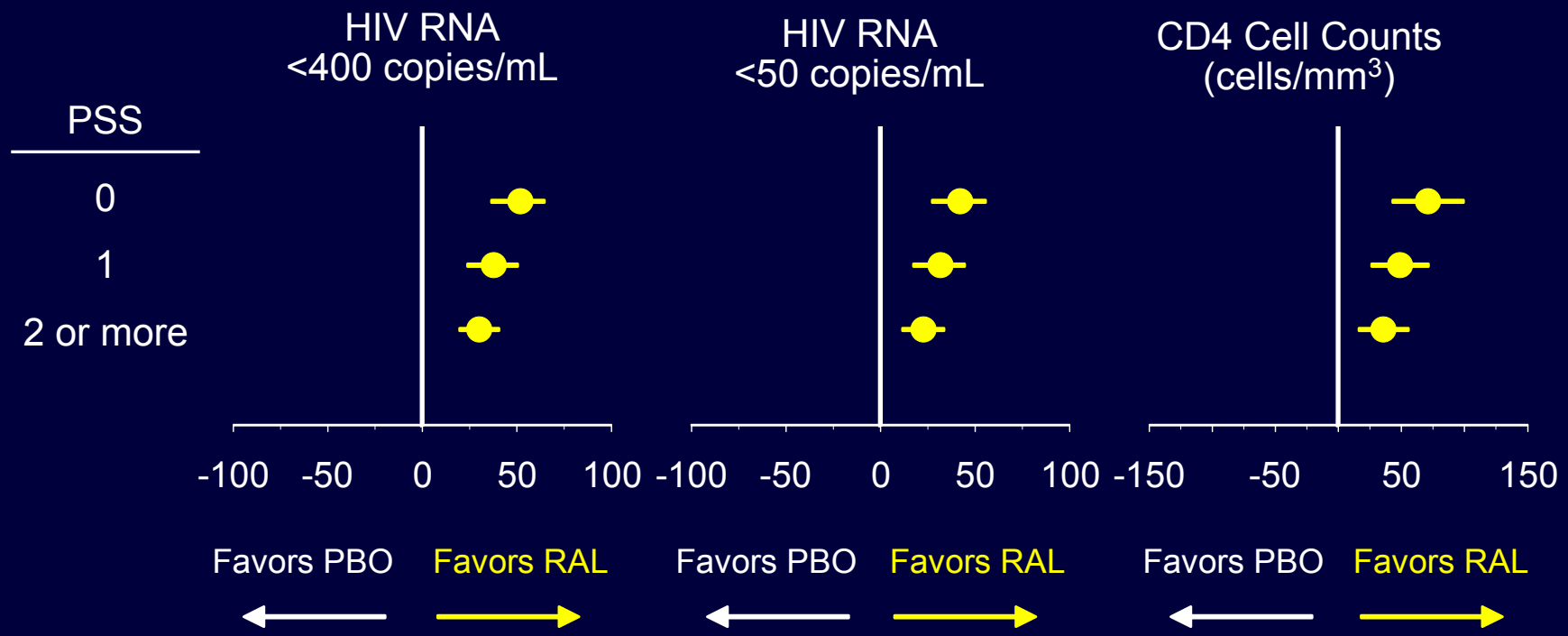
P004 Patient With No Integrase Change Later Developed Resistance Mutations*



* Data not reviewed by FDA. cp/ml = copies per mL. Rx = treatment.

Treatment Effects at Week 24 by Phenotypic Sensitivity Score – Protocols 018 and 019 Combined (Complete Week 24)

Treatment Difference (Raltegravir - Placebo) (95% CI)



PSS = phenotypic sensitivity score.
Baseline carried forward for virologic failures. RAL = raltegravir. PBO = placebo.