

IDX899 - A Novel Once-a-day Second Generation NNRTI for the Treatment of HIV/AIDS

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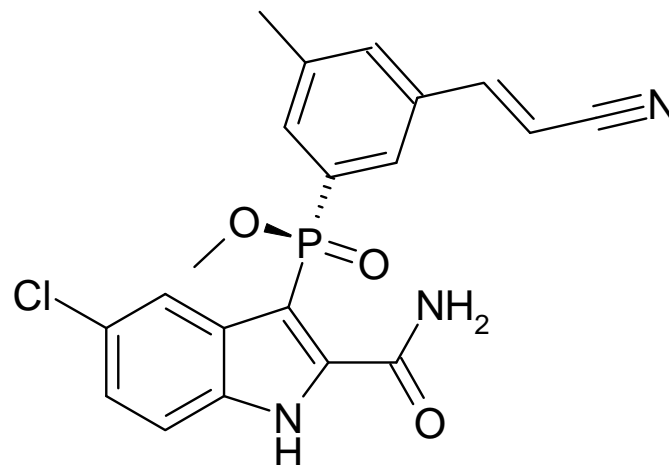
**HIV DART 2008
Rio Grande, Puerto Rico**

Unmet Needs for Next-Generation NNRTIs

- Increased or comparable antiviral efficacy to standard of care (efavirenz)
- Improved resistance profile / higher barrier to resistance (active versus K103N, Y181C, and double mutant)
- Improved safety and tolerability (less CNS side effects, less rash, no liver toxicity)
- Convenient once-daily oral for treatment-naïve
- Toxicity profile consistent with use in women of child-bearing potential
- Minimal drug-drug interactions

IDX899 Background

- Potent and selective inhibitor of wild type and NNRTI-resistant HIV-1 *in vitro**
- High barrier to resistance *in vitro**
- Once-a-day dosing



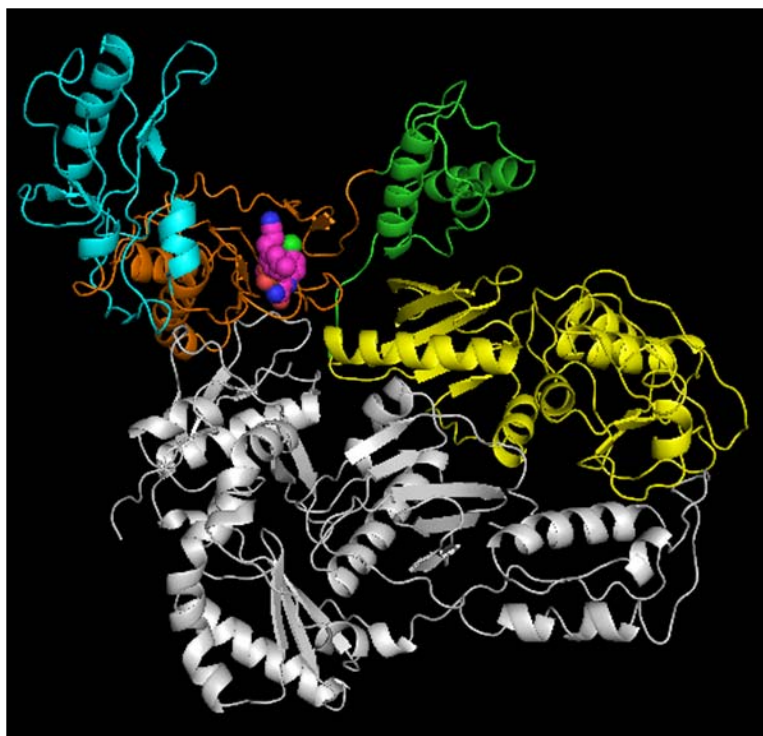
IDX899

$C_{20}H_{17}ClN_3O_3P$
Mol. Wt.: 413.8

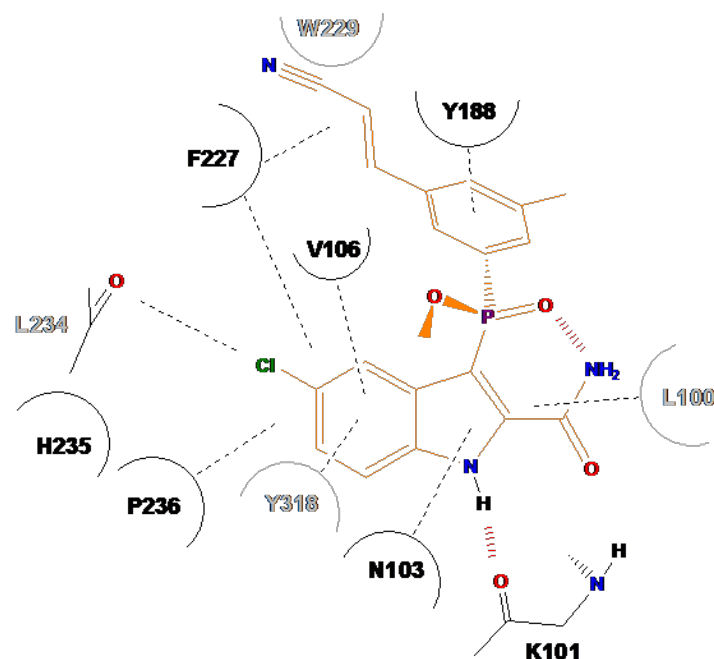
*Richman *et al.* CROI 2007

IDX899 Preclinical Profile: Mechanism of Action

IDX899 binds in the hydrophobic NNRTI pocket

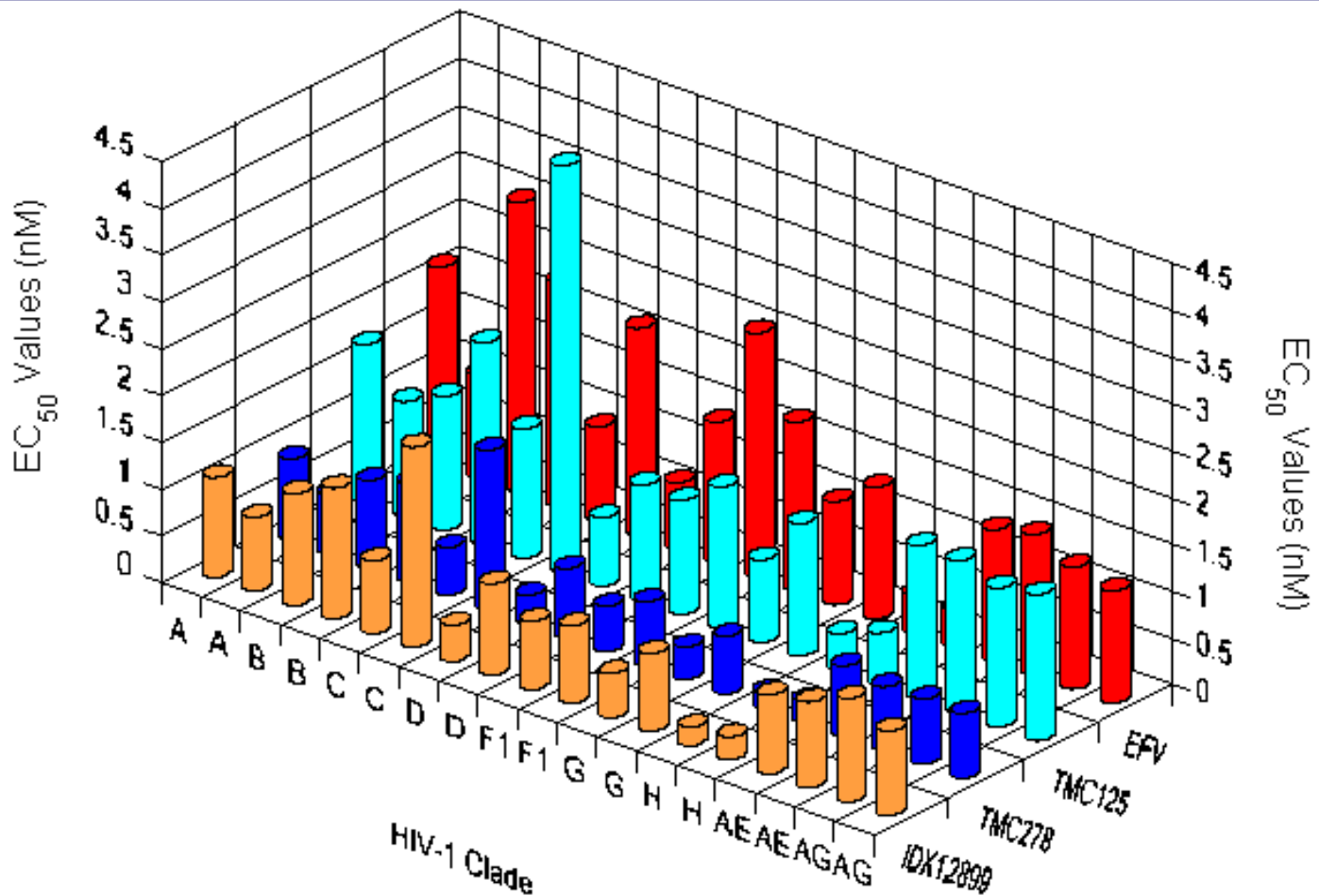


Structure of the
IDX899/HIV-1 RT
co-complex



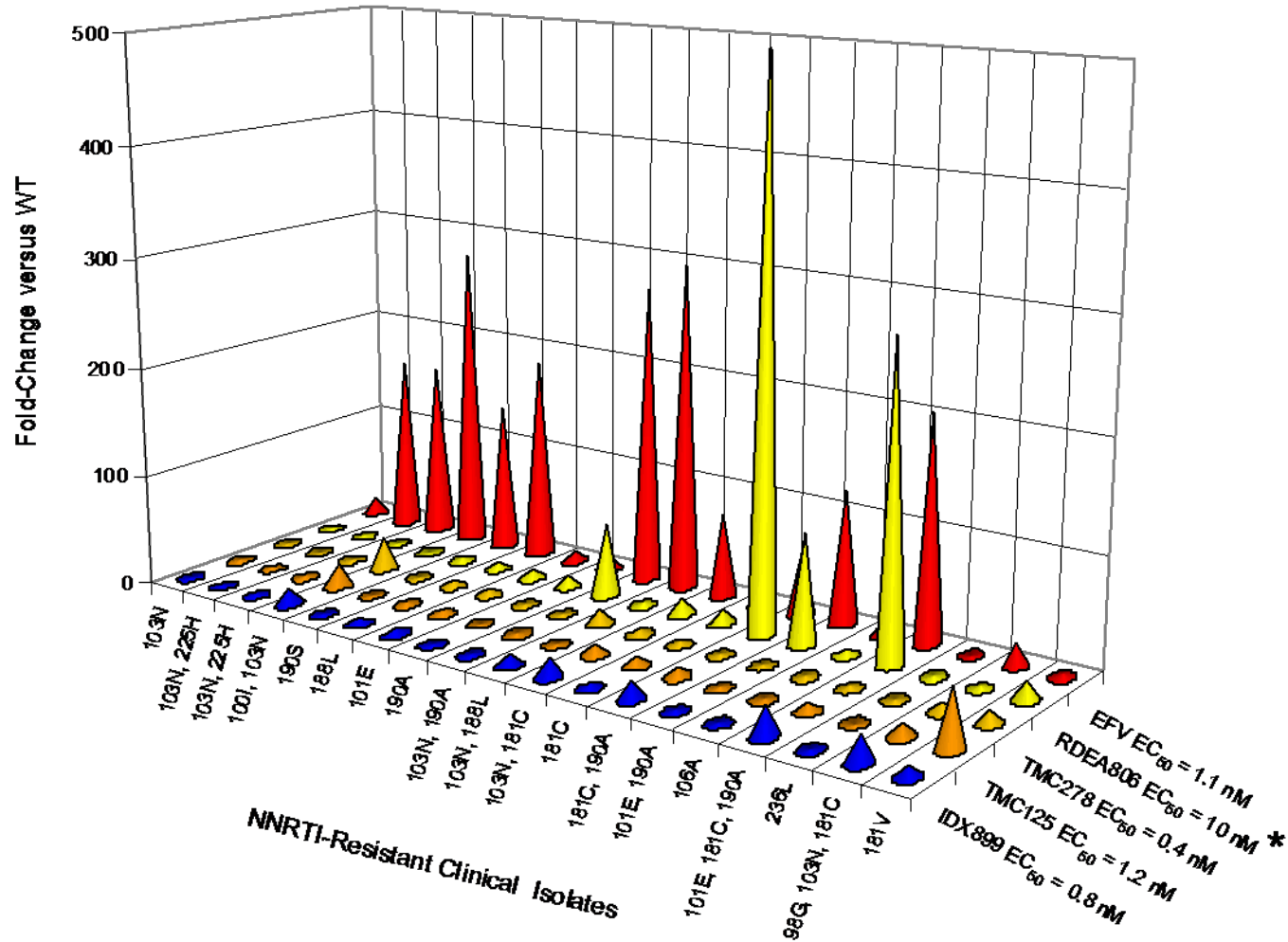
Schematic of the binding
mode of IDX899 to the double
mutant RT

IDX899 Preclinical Profile: Antiviral Activity Against HIV-1 Subtypes



Active against all major HIV-1 subtypes (A, B, C, D, F1, G, H, AE, and AG) with EC₅₀ ranges of 0.2 to 2.14 nM

IDX899 Is Active *In Vitro* Against NNRTI-Resistant HIV-1 Clinical Isolates



Resistance profiling was performed by Monogram Biosciences using the PhenoSense™ HIV

*Ardea Biosciences Abstract #1662, 47th Annual ICAAC, Sept 2007.

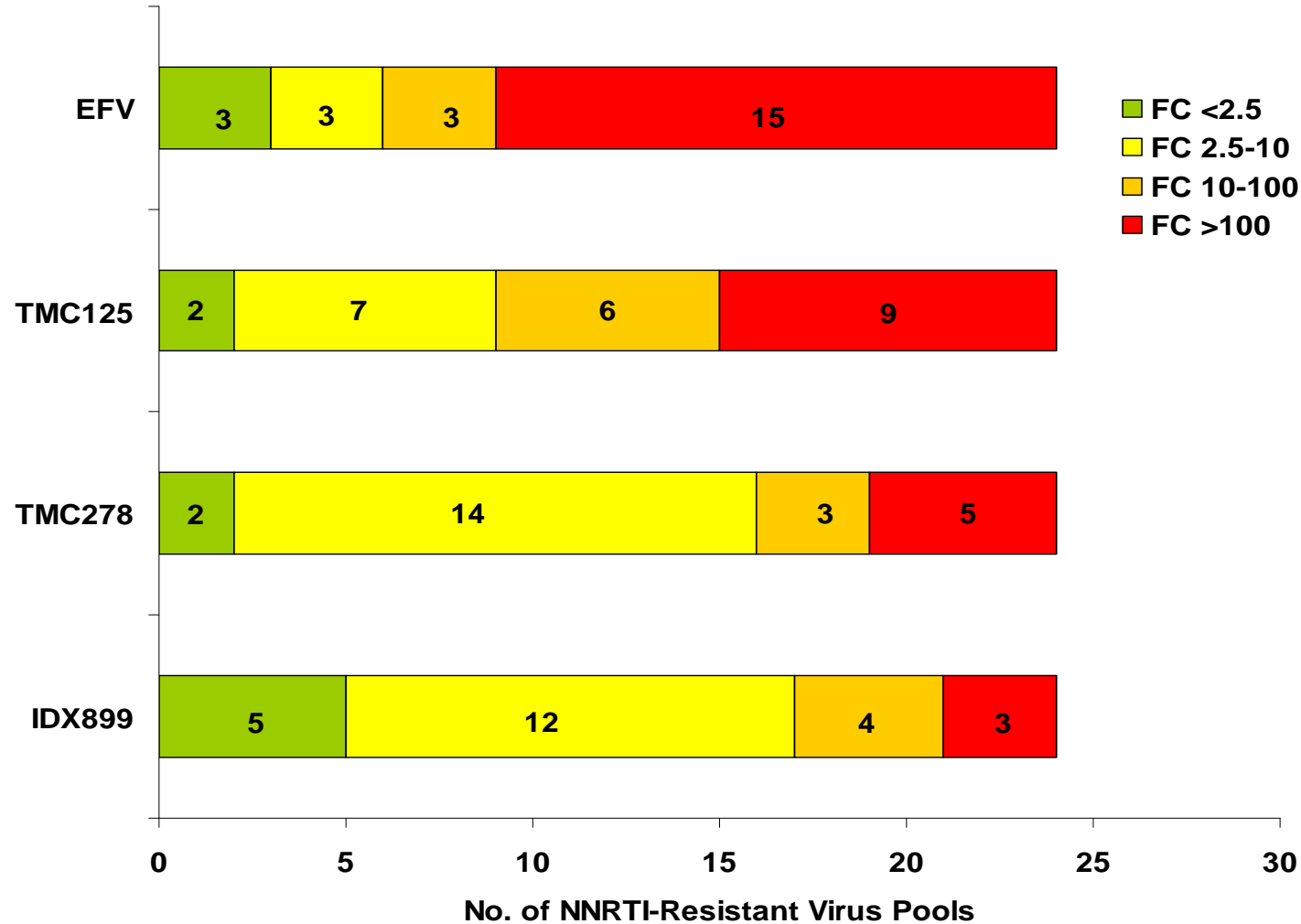
Cross Resistance Profile of IDX899-Selected Virus Pools (Fold Change from Wild-type)

	Experiment 1			Experiment 2				Experiment 3
Passage #	5	13	31	17	23	29	32	32
IDX899 selected mutations*	E138K	E138K, Y181I	E138K, Y181I, M230L	V90I, Y181C	V90I, S134I, Y181C	V90I, S134I, Y181C, M230L	V90I, S134I, I135R, Y181C, M230L	E138K, G190E, L214F
IDX899	3.1	25.9	>1136	8.5	4.7	343.0	172.5	20.2
TMC125	3.0	114.5	>2,500	64.9	6.8	1432.7	685.2	12.7
TMC278	5.2	207.4	>1136	9.4	6.6	320.1	331.5	5.6
EFV	3.7	1.4	132.5	37.6	11.7	306.4	238.9	3.5

Values are derived from a single experiment.

*Mutations selected in the clinic may differ from *in vitro*-selected mutations

Cross Resistance Profile of 24 NNRTI Selected Virus Pools: Overall Summary

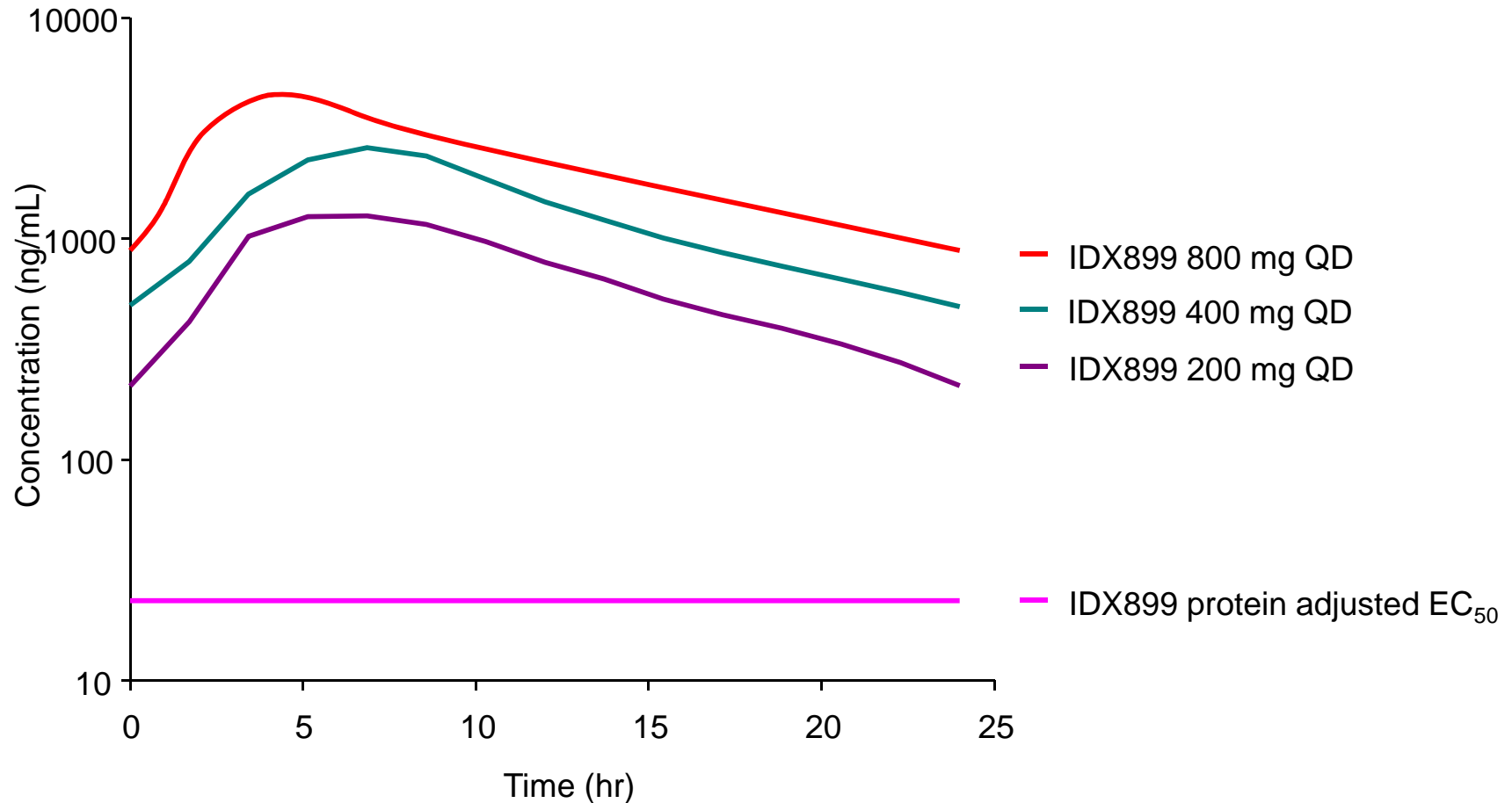


FC = Fold change from wild-type HIV-1_{BH10} virus

IDX899 Clinical Development Program: Phase I/IIA

- NV-05X-001 Single dose micro-dosing study (completed)
 - IDX899 selected for clinical evaluation
- NV-05A-001 Phase Ia rising single doses followed by 7-day multiple doses in healthy volunteers (completed)
 - Rising single-dose with food in healthy males at 200, 400, 800 and 1200 mg
 - Single dose PK in healthy females of non-child bearing potential
 - 7-day multiple dose in healthy males of 800 mg PO QD and 400 mg PO BID
- NV-05A-002 Phase Ib/IIa 100, 200, 400 and 800mg QD vs placebo x 7 days in HIV-infected treatment-naïve men and non-child bearing women (completed)
 - Primary outcome measurement – change in HIV RNA from Baseline after 7 days dosing
 - Intensive PK following the first and last doses within each cohort
- NV-05A-003/004 (completed)
 - DDI studies with Truvada (28 healthy volunteers) and Atazanavir (18 healthy volunteers)

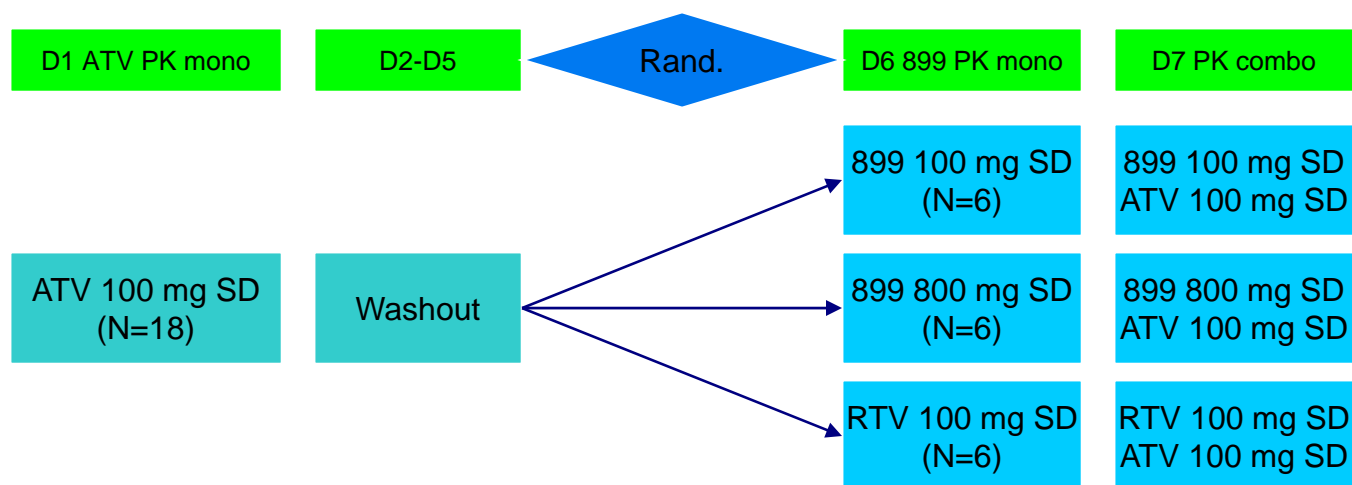
IDX899 Exhibited Excellent Drug Exposure Dosed Once-a-Day



NV-05A-001 Summary

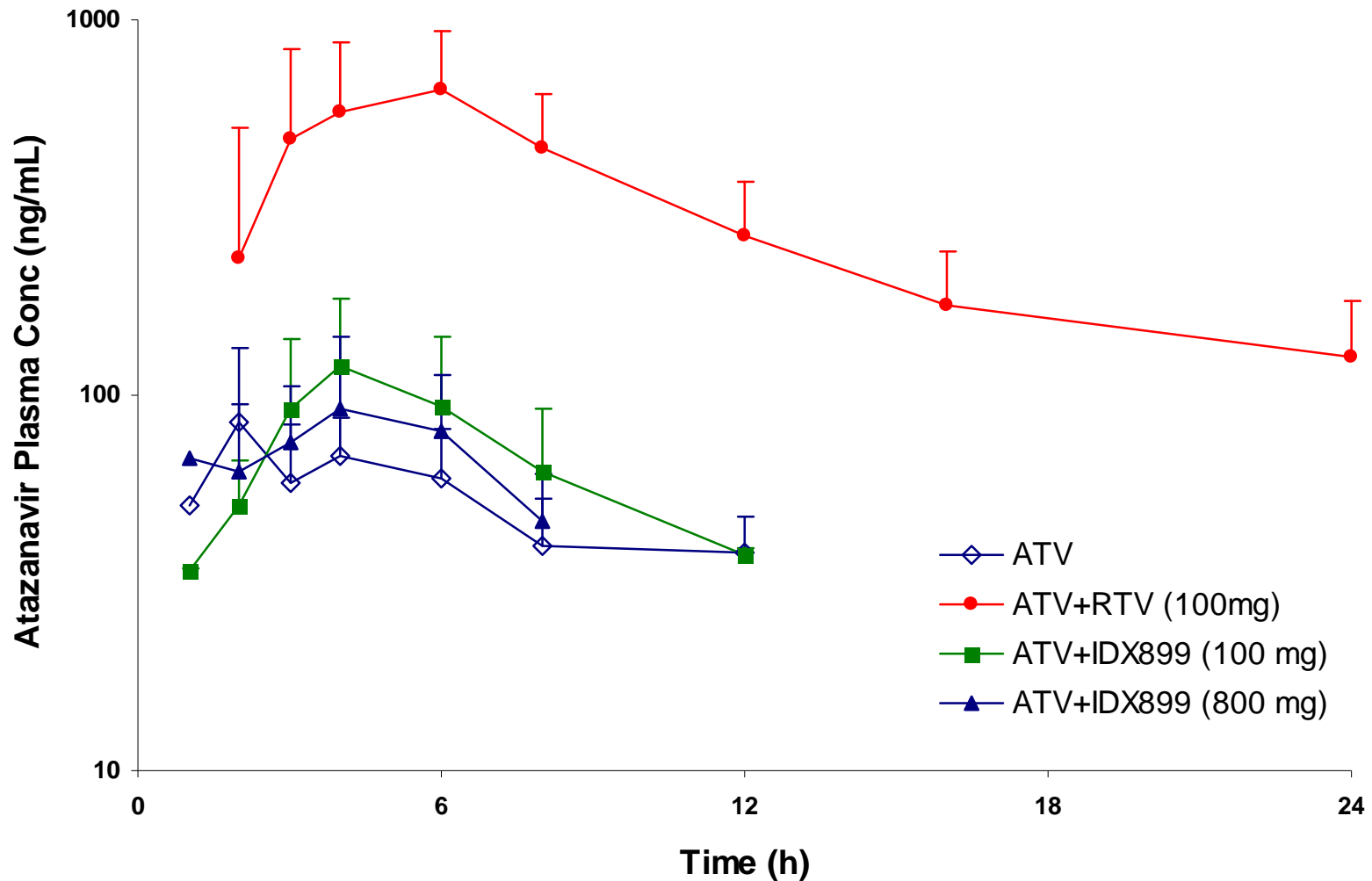
- Well tolerated with no SAEs or patterns of adverse events
- Dose proportional plasma drug exposure
- Positive food effect (2X increase in drug exposure)
- No evidence of dose accumulation or induction with 7 day QD dosing
- Steady-state trough concentrations were well above the protein binding adjusted EC_{90} (110 nM or ~50 ng/mL)
- Propose to dose QD for treatment-naïve patients and patients with NNRTI-resistant virus

NV-05A-003: IDX899/Atazanavir (ATV) Boosting Study Design



*Subjects randomized to RTV did not have PK performed for RTV on day 6 or day 7.
RTV = ritonavir

NV-05A-003: PK of ATV in the presence of IDX899



NV-05A-004: IDX899/Truvada[®] Study Design

28 healthy male or female subjects

Group A
(N=12)

Truvada[®]
Days 1-14

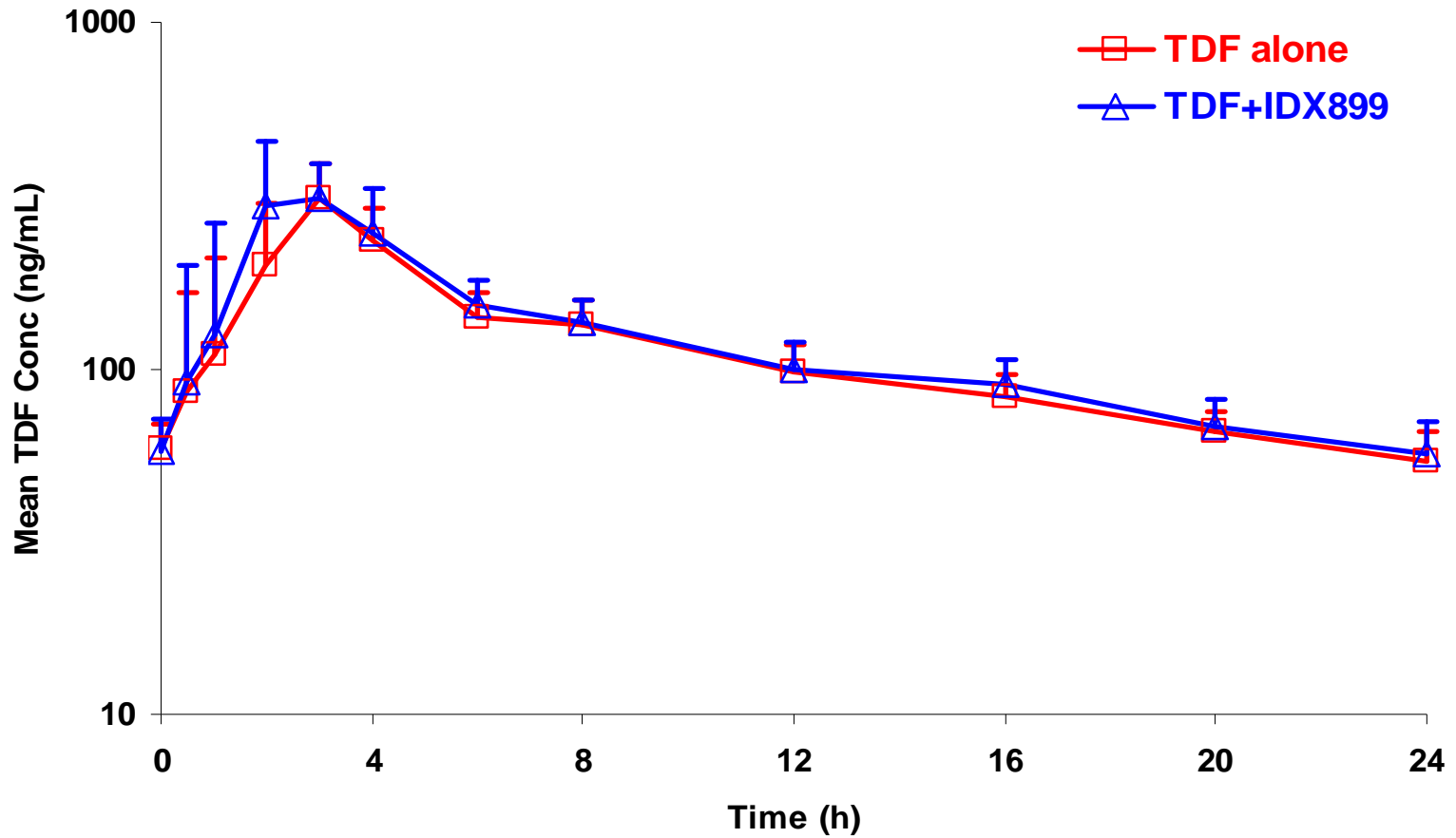
IDX899 800 mg Days 8-14

Group B
(N=16)

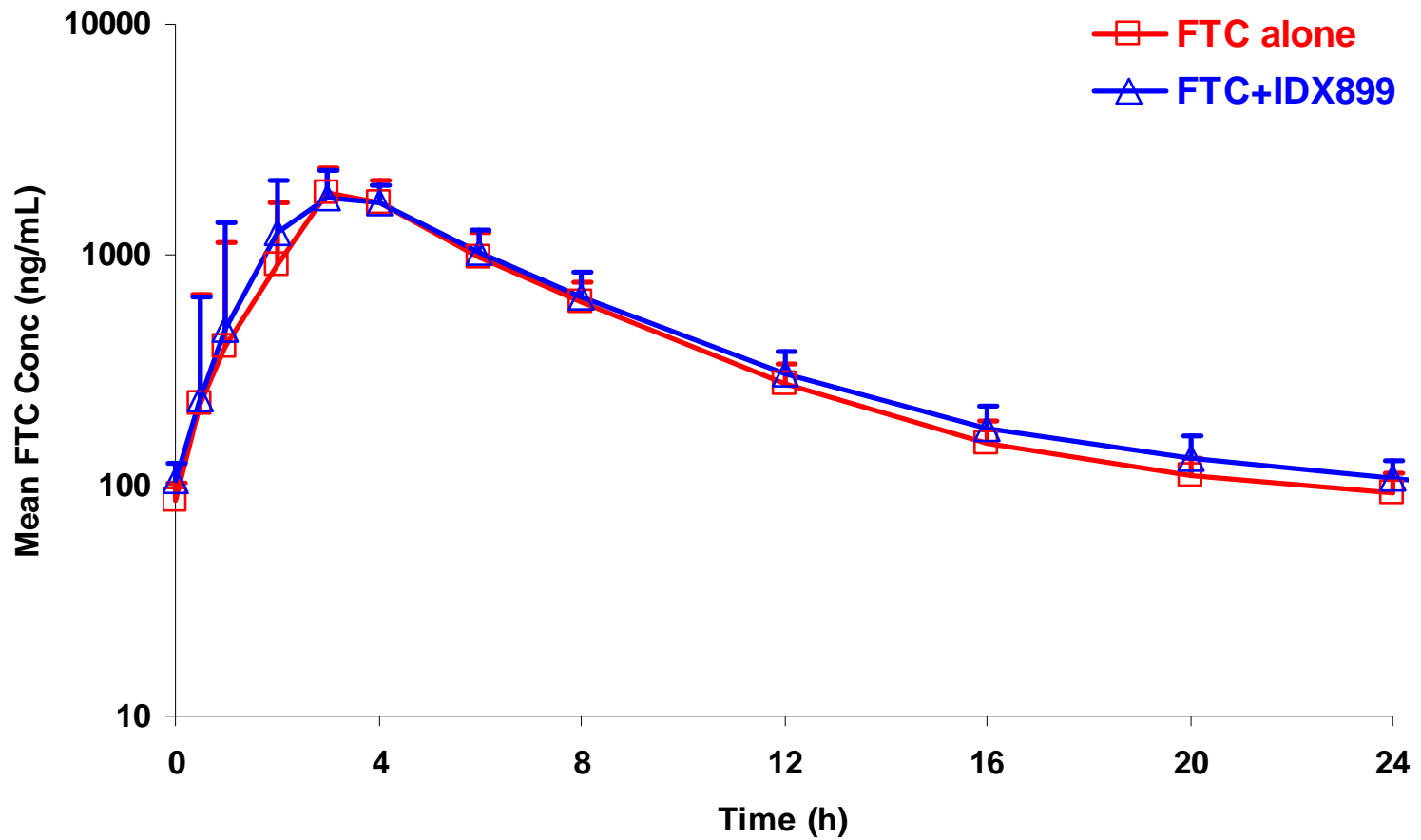
Placebo
Days 1-7

IDX899 800 mg Days 8-14

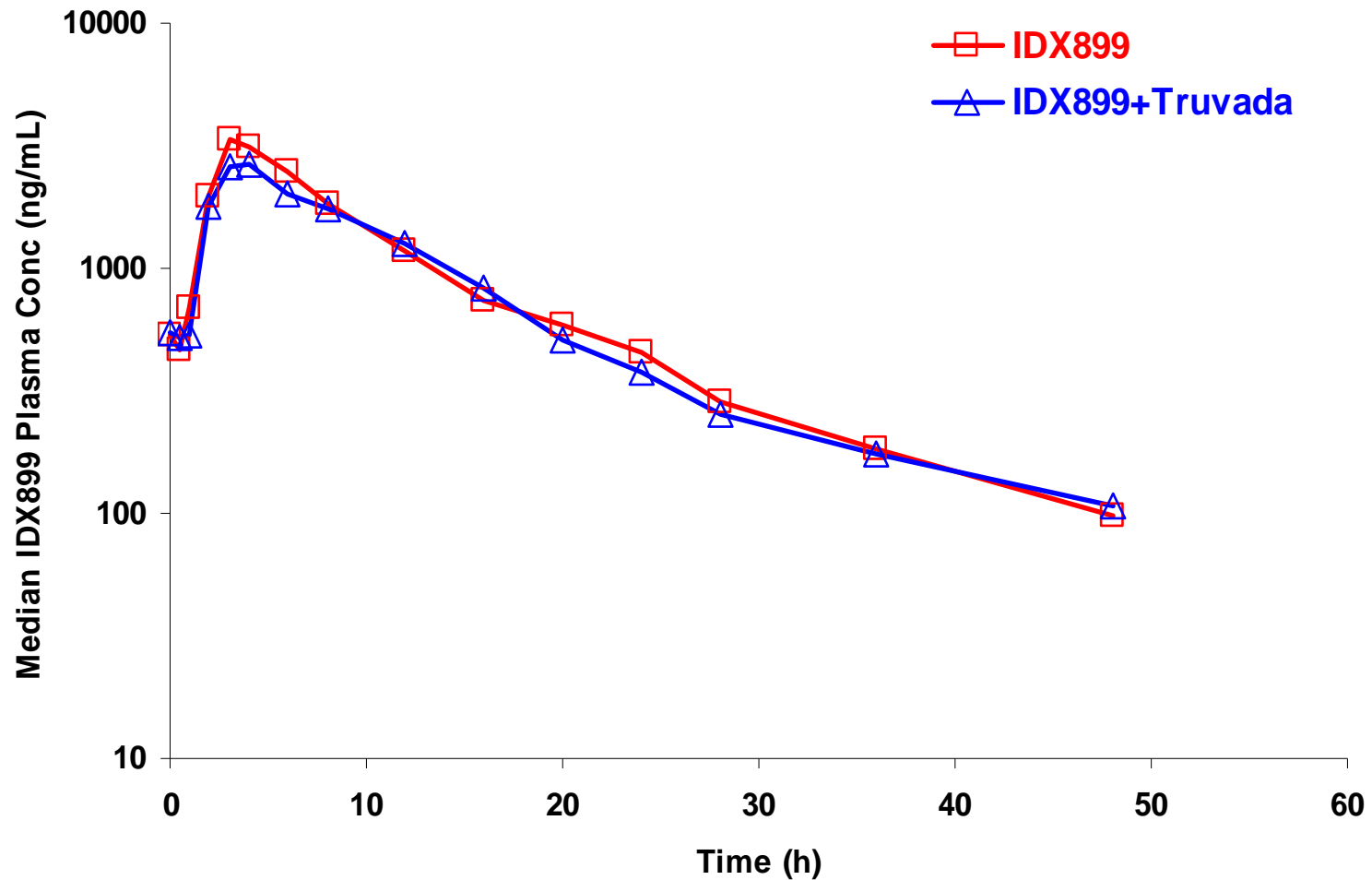
NV-05A-004: PK of tenofovir in presence of IDX899



NV-05A-004: PK of emtricitabine in presence of IDX899



NV-05A-004: PK of IDX899 in presence of Truvada[®]



NV-05A-002: Proof-of-Concept Study

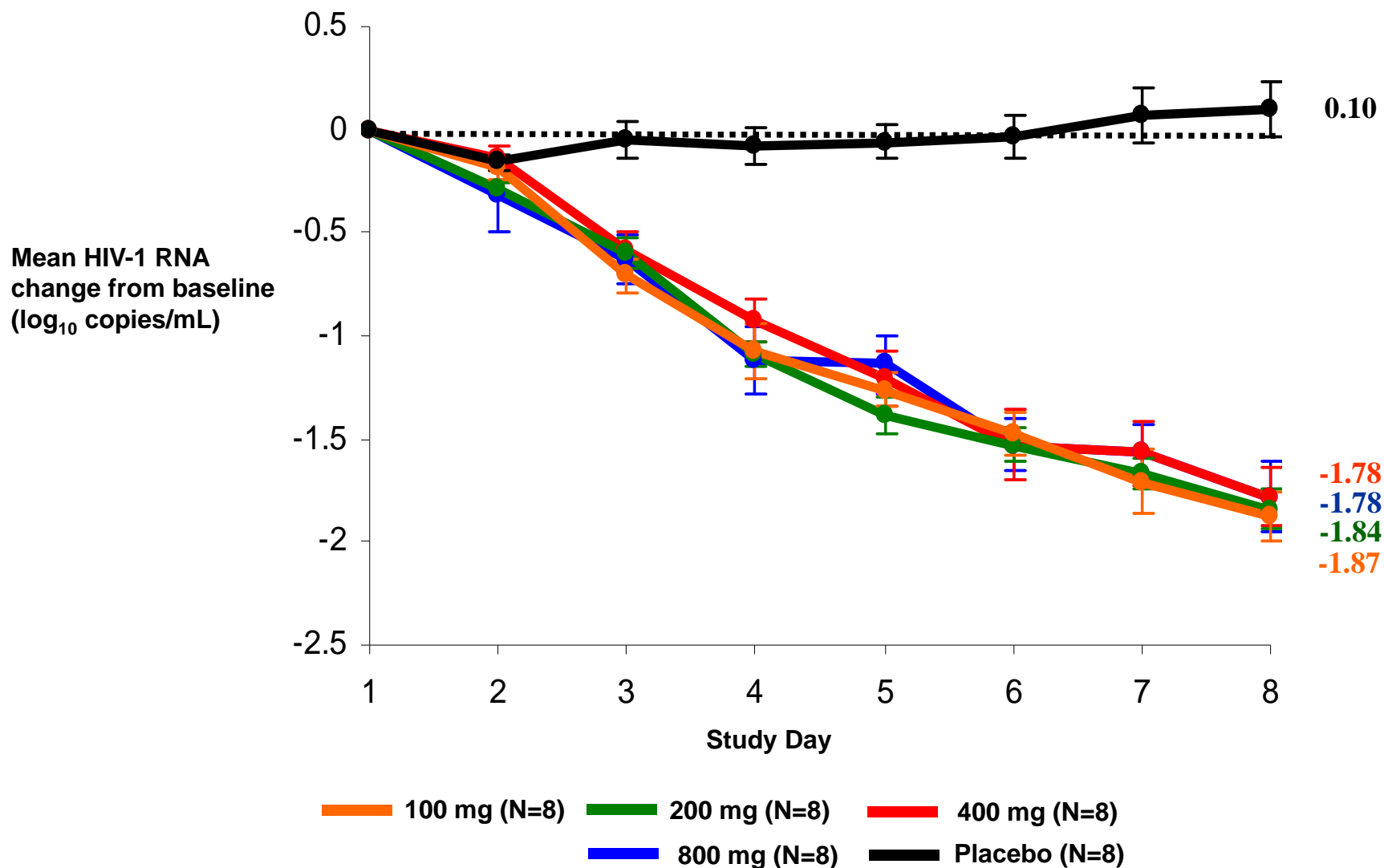
- Study Design:
 - Single-center, sequential cohort, double-blind, placebo-controlled study in treatment-naïve HIV-1-infected subjects
 - Randomized 8:2 (IDX899:placebo)
 - 4 dose cohorts (800 mg, 400 mg, 200 mg, 100 mg; QD)
 - 7 day treatment period
 - Eligible subjects placed on Kaletra[®] monotherapy for 28 days or HAART following last IDX899 dose

- Objectives:
 - Safety and tolerability, antiretroviral activity, PK/PD

NV-05A-002: Baseline Characteristics

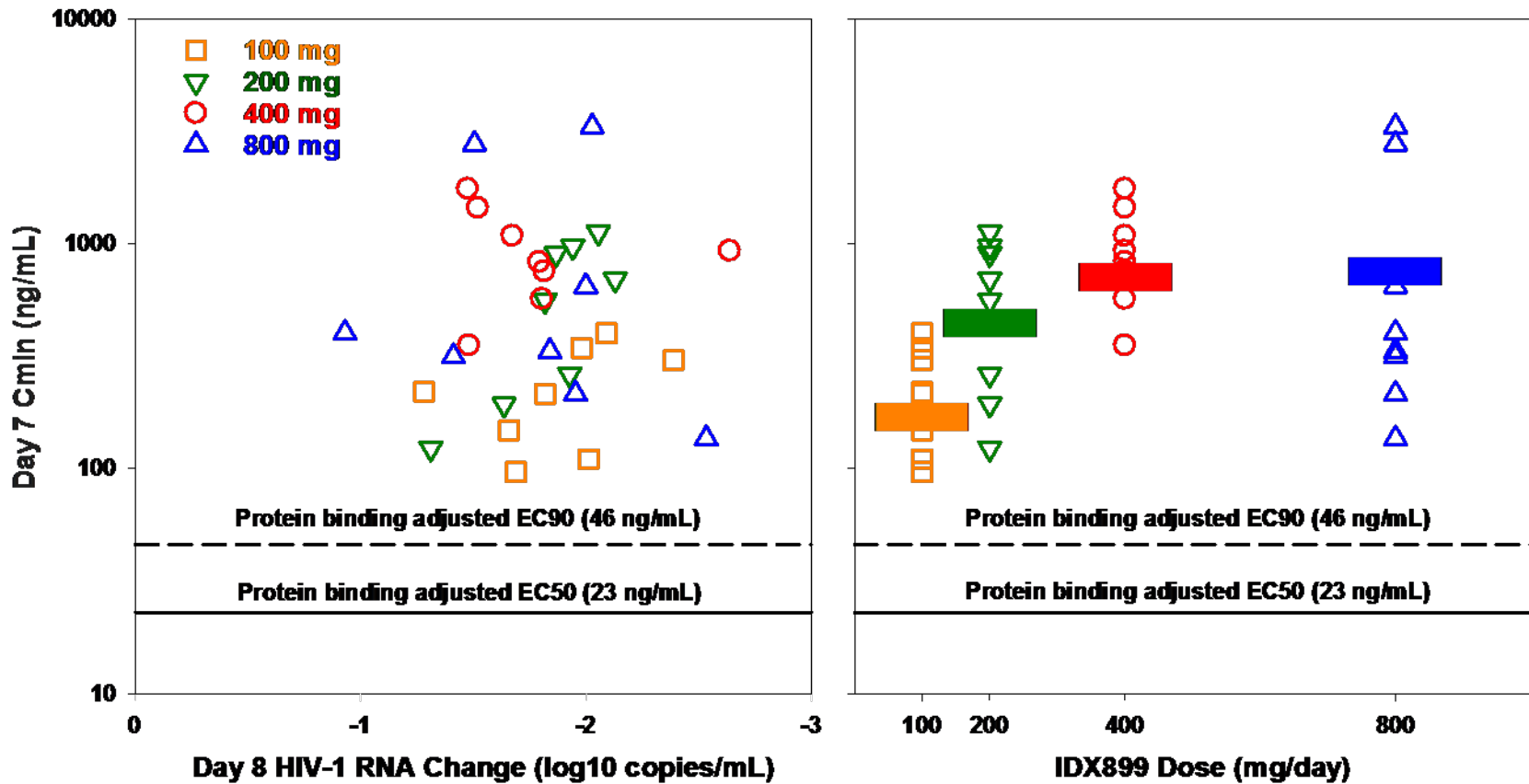
	IDX899				Placebo
	100mg N=8	200mg N=8	400mg N=8	800mg N=8	N=8
Age					
Mean years	33.3	29.9	33.9	32.4	35.5
Sex, n					
Female	0	0	0	2	1
Male	8	8	8	6	7
Race, n					
Caucasian	0	0	1	0	0
Hisp./Latino	8	8	7	8	8
Weight					
Mean kg	70.8	78.1	73.5	64.4	72.3
CD4⁺ count					
Mean cells/ μ L	491.4	432.4	466.1	436.8	567.1
HIV-1 RNA					
Mean (log ₁₀ copies/mL)	4.81	4.74	5.09	4.36	4.54

NV-05A-002: HIV-1 RNA Change from Baseline (Amplicor[®] 1.5 Assay)



NV-05A-002: IDX899 Pharmacokinetics

- No clear PK/PD relationship was observed



On-treatment Adverse Events (in ≥ 2 subjects)

	IDX899				Placebo
	100 mg N=8	200 mg N=8	400 mg N=8	800 mg N=8	N=8
Headache	3	2	3	2	4
Dyspepsia	3	1	2	0	3
Nausea	0	1	1	1	1
Back pain	1	0	1	1	0
Toothache	0	2	0	1	0
Abdominal pain	1	0	0	0	1
Anxiety	0	0	1	1	0
Constipation	1	0	0	0	1
Diarrhea	0	0	1	0	1
Ear pain	0	0	0	0	2
Neck pain	0	1	0	1	0
Pain in extremity	0	0	2	0	0
Tooth infection	0	1	0	1	0

NV-05A-002 Safety Summary

- No treatment-emergent SAEs or premature discontinuations
- No discernable patterns in adverse events between treatment groups
- No grade 3 or 4 laboratory abnormalities during IDX899 treatment period
- Laboratory profiles similar between IDX899 groups and placebo

IDX899 Clinical Overview: Conclusions

- IDX899 was generally safe and well tolerated in healthy and HIV-1-infected subjects.
 - No SAEs and no discernable pattern of adverse events or laboratory abnormalities were observed.
- Food enhanced absorption of IDX899; no gender effect was observed.
- When combined with IDX899, atazanavir and Truvada[®] pharmacokinetic parameters were not markedly altered.
- IDX899 demonstrated potent antiviral activity, mean 1.8 log₁₀ reductions, at all tested doses in treatment-naïve patients.
- No clear PK/PD relationship was demonstrated, likely due to drug trough levels well above the EC₉₀ of IDX899 against wild-type viruses.
- IDX899 is a promising, second generation, once-daily NNRTI for the treatment of HIV-1 infected subjects.

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