

RDEA806, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, Shows Positive Outcome in Treatment of Naïve HIV Patients

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48th Annual ICAAC/IDSA 46th Annual Meeting

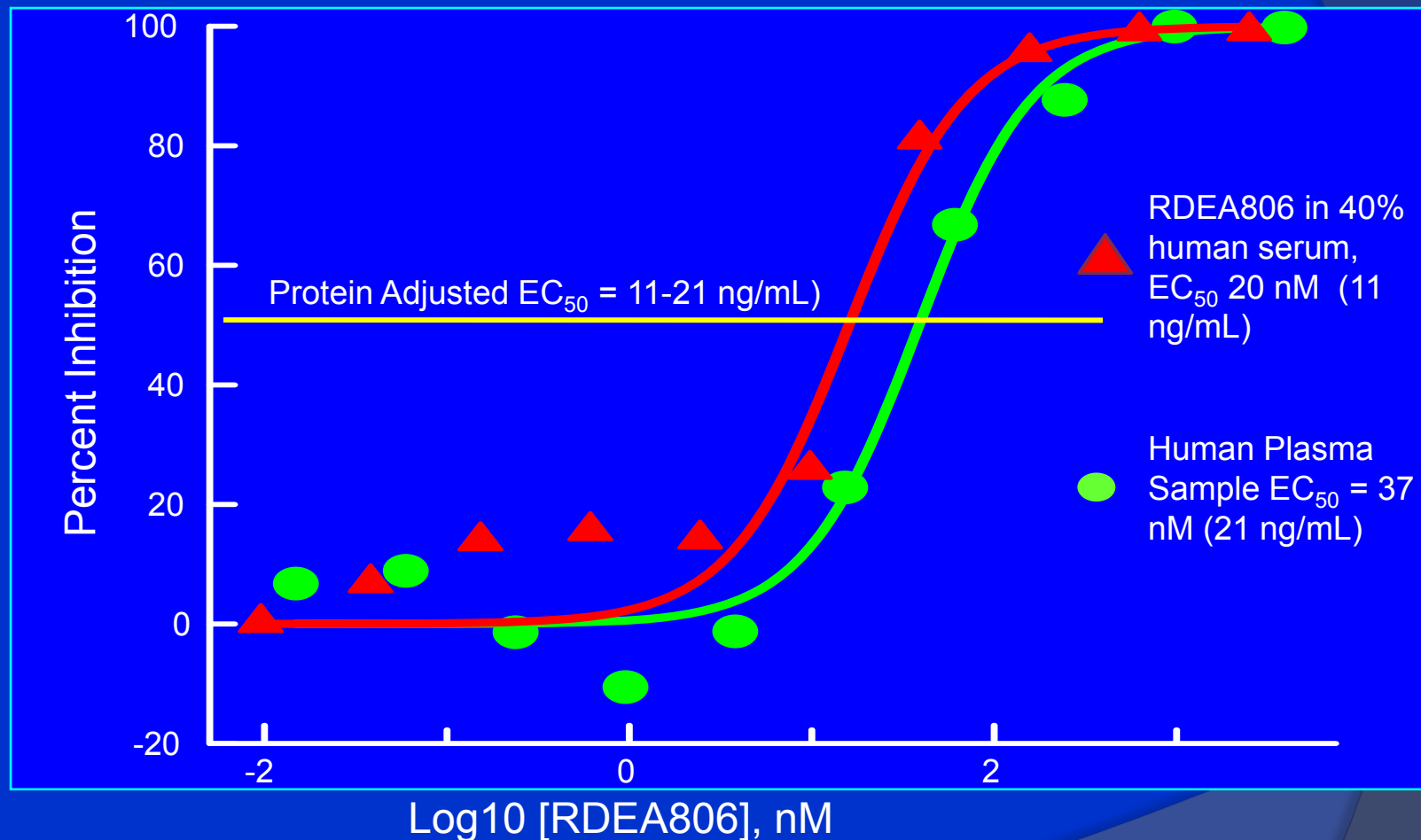
25-28 October 2008

Washington, DC

Preclinical Background

- RDEA806 is a potent ($EC_{50wt} = 3 \text{ nM}$), selective HIV NNRTI designed to maintain activity against the most common mutations observed with efavirenz ($EC_{50K103N} = 2.3 \text{ nM}$)
- High barrier to resistance
- Cytotoxicity selectivity index $> 9,000$
- Highly protein bound ($\sim 99.5\%$)
- Limited metabolism by CYP450 (none by 2B6) and no inhibition or induction of CYP450
- Completed animal reproduction studies have shown no evidence of teratogenicity or impairment of fertility
- Highly water soluble, allowing for preparation of easy to swallow tablets

In Vitro Antiviral Activity of RDEA806 in Human Plasma PK Sample



The in vitro antiviral activity of RDEA806 in human plasma taken after 10 days of 400 mg dosing was measured in the VSVg-pseudotyped, single cycle infection system. Activity from a titration of this sample into 40% human serum was compared with activity from a titration of RDEA806 in 40% human serum and is shown in the dose response inhibition curve. Hamatake, et al. Poster #731 CROI February 2008

Study 201 Proof of Concept Study Design

- Multi-center, double-blind, placebo-controlled study in treatment-naïve HIV-1-infected subjects
- 48 patients randomized 3:1 (RDEA806:placebo)
- 7-day treatment period plus am dose for pk on day 8
- 4 sequential dose cohorts:

Capsules	EC Tablets
400 mg BID Fasted	800 mg QD Fed
600 mg QD Fasted	1000 mg QD Fasted

- Assessments
 - HIV RNA, PK and tolerability Days 1-10 & 2 wks post-dose
 - Safety labs, immunology Days 1, 4, 9 & 2 wks post-dose
 - ECGs Days 1, 3, 4, 7, 9 and 2 wks post-dose
 - Genotype and phenotype Days 1, 9 & 2 wks post-dose

Study 201 Patient Population

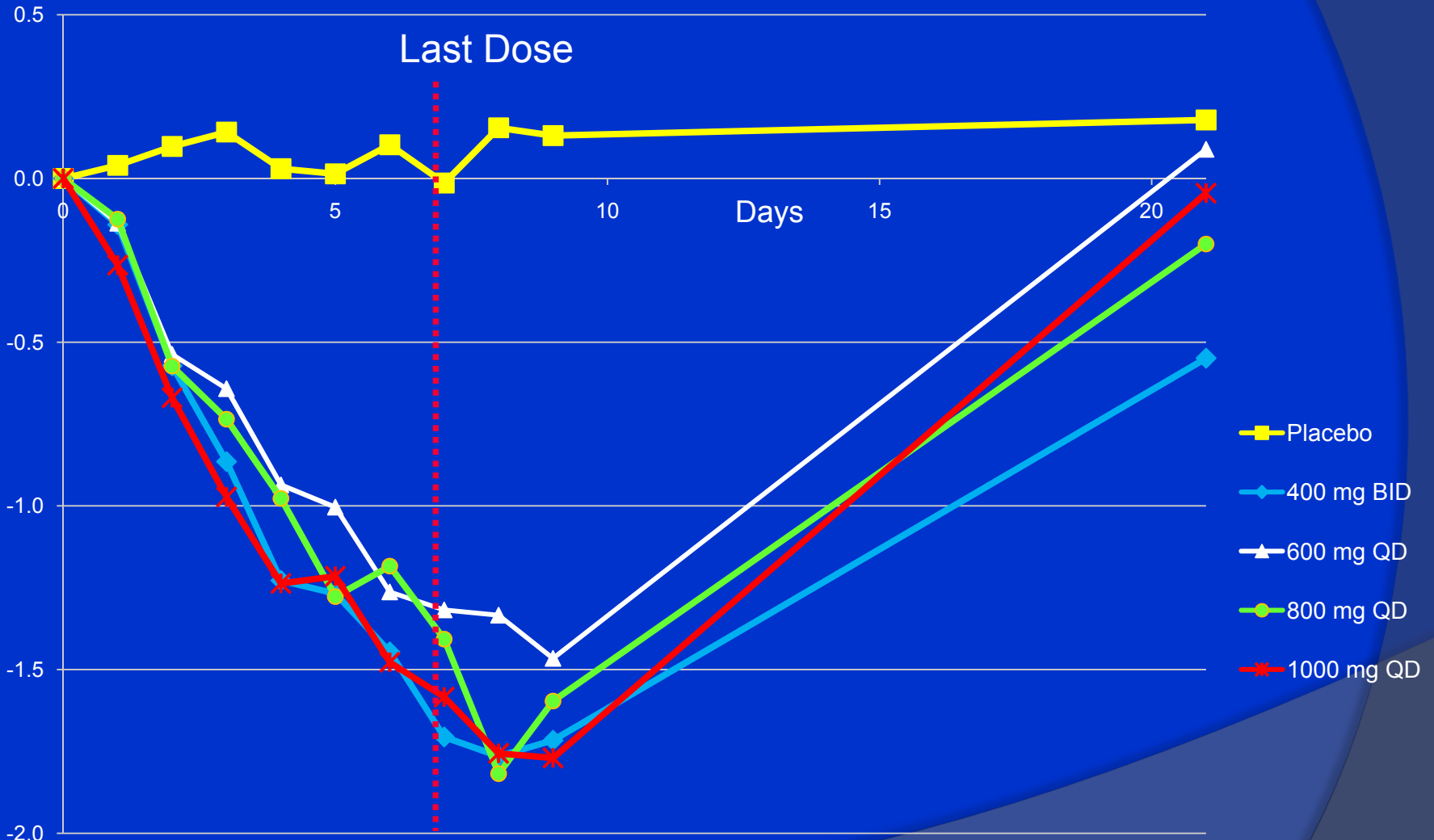
- Male patients
- 18-65 years
- Chronic HIV infection
- Antiretroviral treatment naïve or < 14 days prior therapy
- HIV RNA $\geq 5,000$ copies/mL
- CD4+ cell count
 - UK: ≥ 50 cells/mm³ in UK for 2 cohorts, then ≥ 200 cells/mm³
 - Germany and Austria: ≥ 350 cells/mm³ in
- No history of AIDS-defining illness
- No pre-existing RTI or PI drug resistance
- No co-infection with acute HAV, chronic HBV, active HCV

Study 201 Baseline Characteristics

	RDEA806				PLACEBO
	400mg BID*	600mg QD*	800mg QD	1000mg QD*	
	N=9	N=9	N=9	N=9	N=12
Age					
Mean years	35.3	39.9	31.2	33.0	36.3
Race					
Caucasian	7	9	7	7	8
Black	2	-	1	2	1
Asian	-	-	-	-	-
Other	-	-	1	-	-
CD4 Cell Count					
Mean cells/mL	288.1	319.9	303.6	407.2	325.9
Viral Load					
Copies/ml	31,815	46,845	40,161	39,852	32,551
Range	4880-113000	6060-879000	15900-244000	7520-469000	5730-233000

* Dosed in fasted state

Median Change in Viral Load*



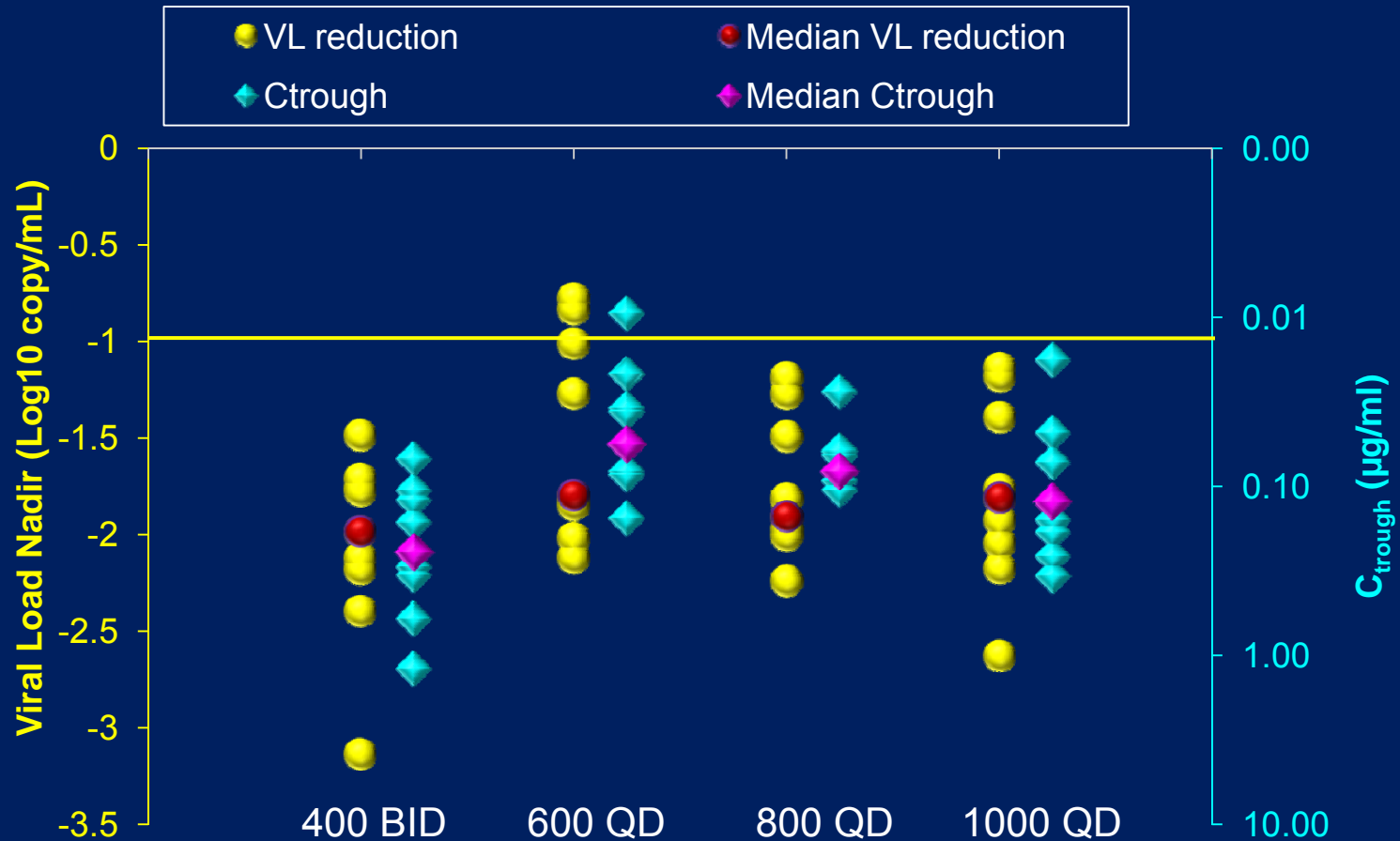
* Viral load reduction censored in 4 patients who reached 50 copies/ml LOQ of assay, and several patients started on triple therapy after Day 10 and prior to follow-up visit

Steady-State Pharmacokinetics

	AUC _{0-24h} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	T _{max} (hr)	t _{1/2} (hr)
400 BID MR capsule Fasted	15.4	4.33	2.11	12.1
600 QD MR capsule Fasted*	7.53	2.98	2.12	8.7
800 QD EC tablet Fed	9.76	2.76	5.67	10.8
1000 QD EC tablet Fasted*	16.1	5.72	3.17	8.5

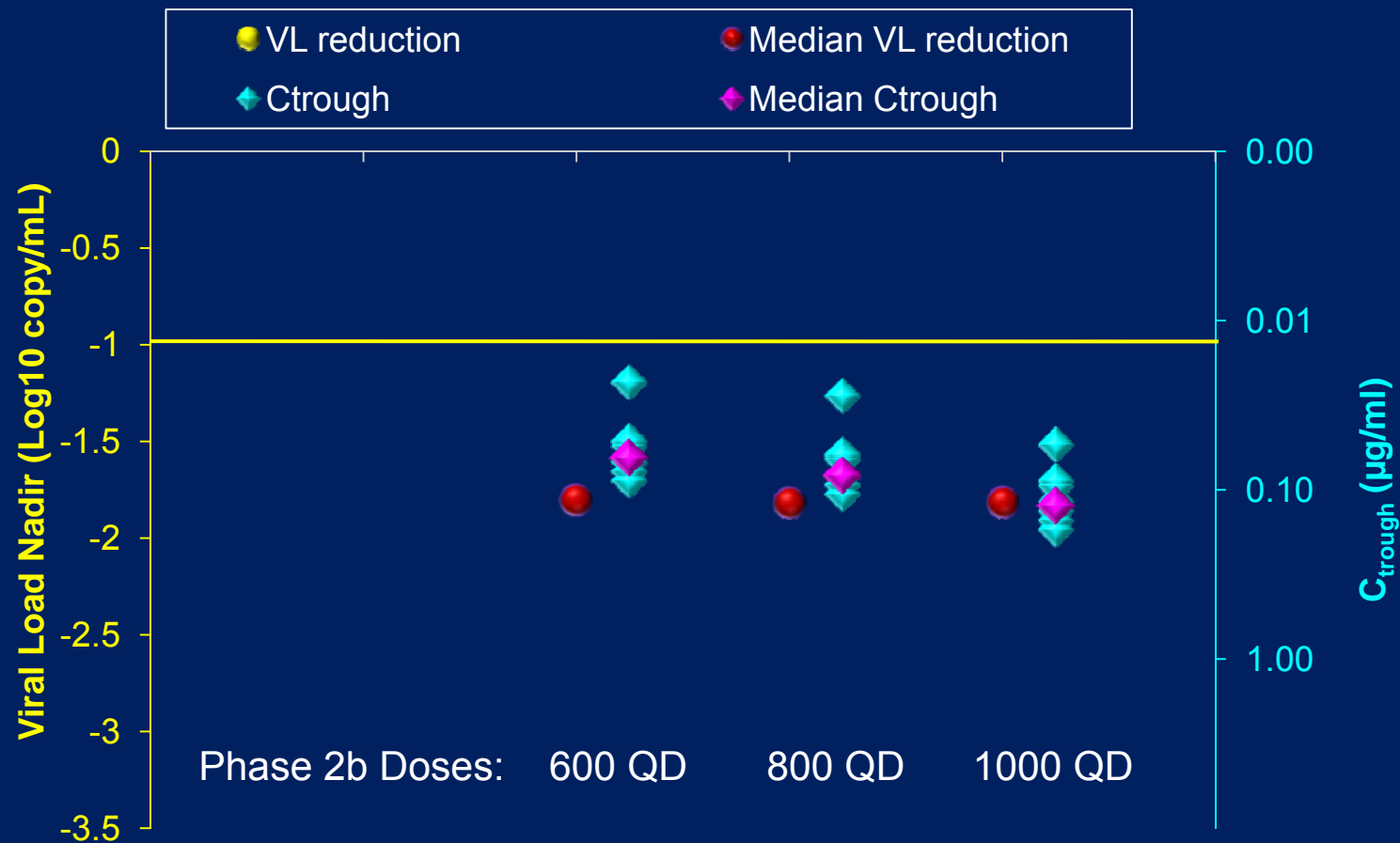
* Dosing of 600 and 1000 mg with the EC Tablet in fed condition planned for Phase 2b study is expected to decrease C_{max} and increase T_{max} and t_{1/2}

Viral Load Reduction and C_{trough} by Cohort



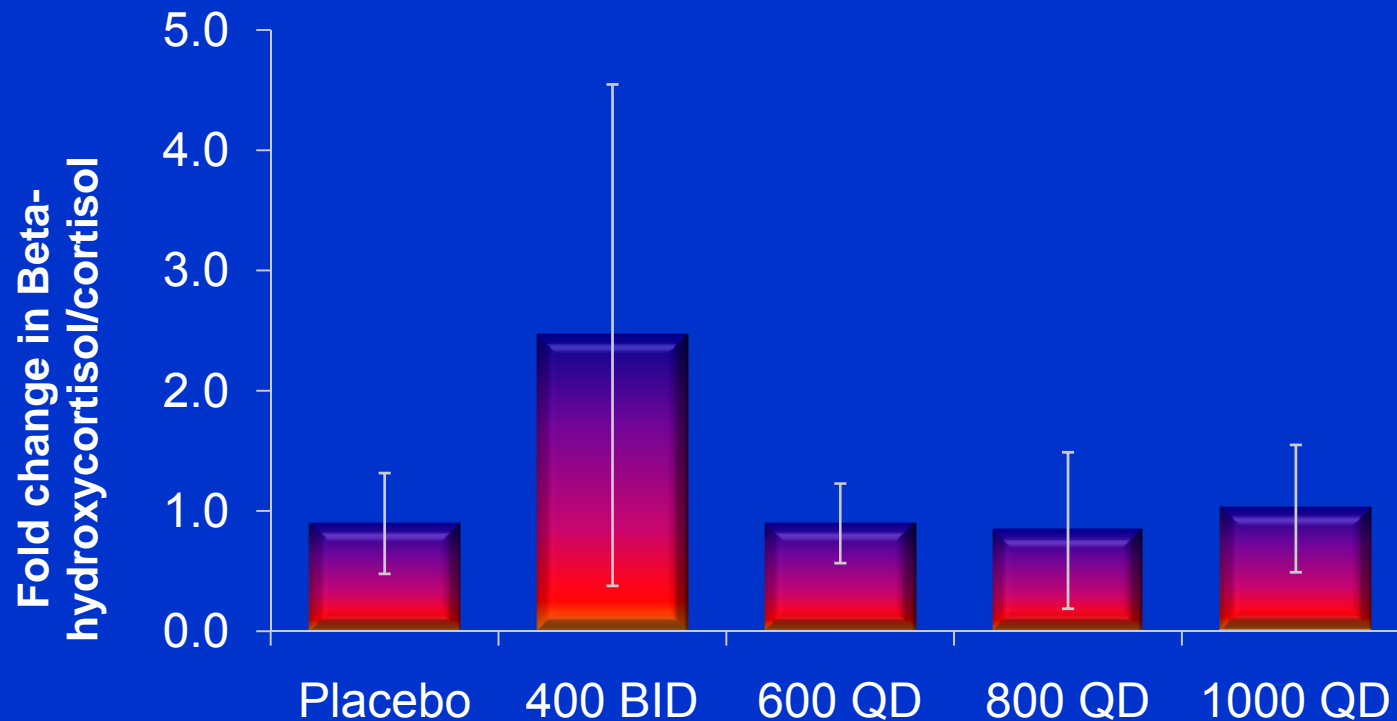
C_{trough} of ~20 ng/mL produced ≥ 1 log reduction in viral load

EC Tablet Given with Food Greatly Reduces Variability



600 mg and 1000 mg doses projected from 800 mg results

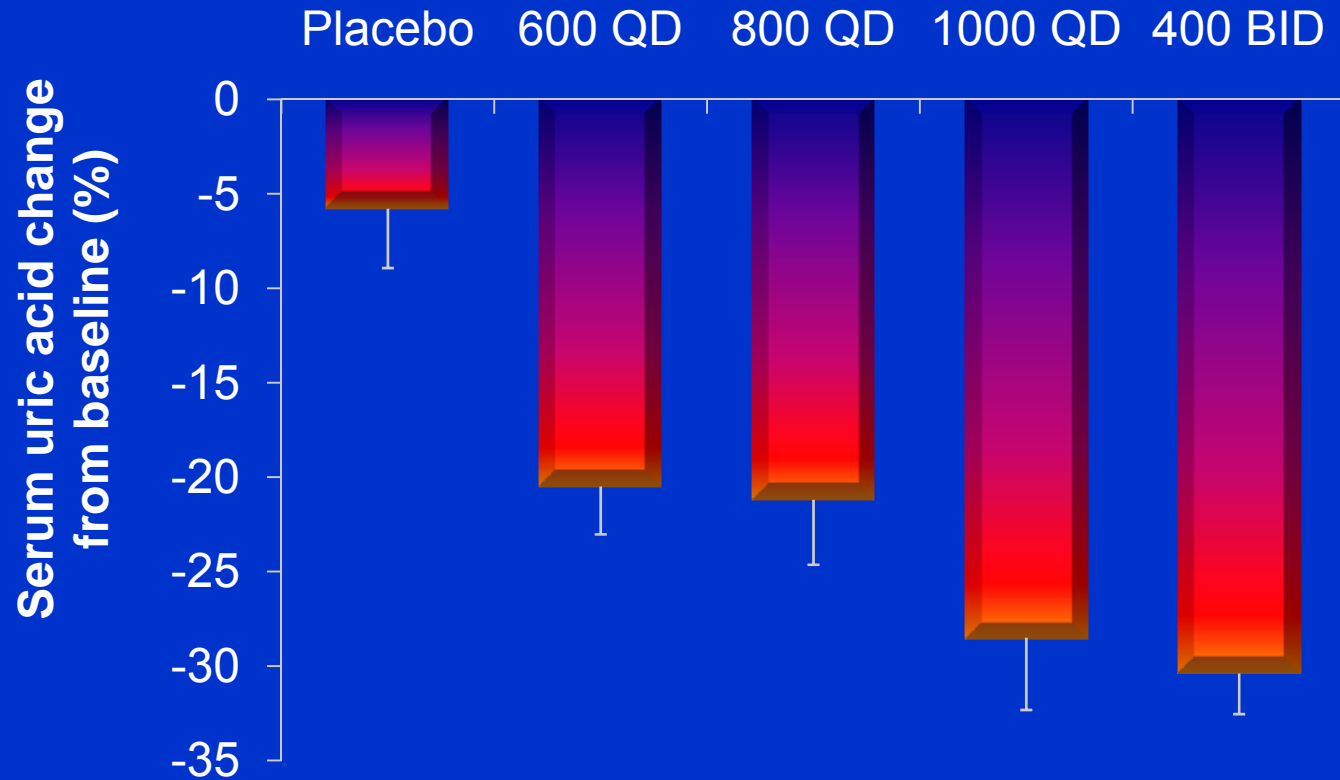
No Significant Induction of CYP3A4 by RDEA806



Mean fold change	0.896	2.46	0.897	0.837	1.02
T-test <i>p</i> vs placebo		0.074	0.994	0.808	0.556

No significant change in beta-hydroxycortisol/cortisol ratio

Significant Serum Uric Acid Reduction



T-test *P* vs placebo

0.0011

0.0010

<0.0001

<0.0001

Mean sUA reduction (%)

-6

-21

-21

-28

-30

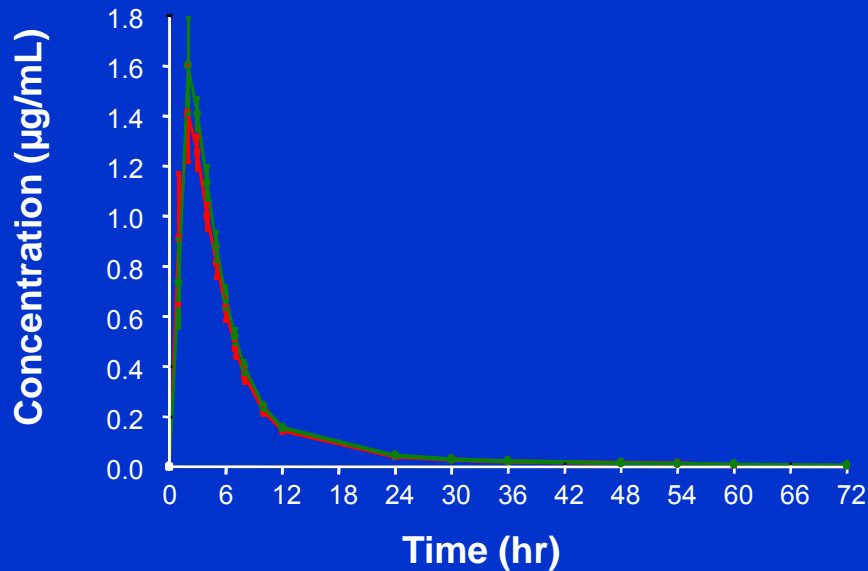
Safety and Tolerability

- No serious adverse events or premature discontinuations
- Adverse events generally mild (grade 1) with no required intervention; no grade 3/4 adverse events
 - No indication of CNS toxicity and no drug related rash
- No clinically significant laboratory abnormalities
 - Reductions in serum uric acid levels (metabolite RDEA594 being developed for gout)
 - No apparent effects on lipid profile
- No clinically relevant ECG findings
 - No QT/QTcF increases >60 msec, nor values > 450 msec
 - QTcF increases of >30 msec were only seen in placebo patients
- No characteristic changes in genotypes or phenotypic susceptibility observed (Poster H-1222)

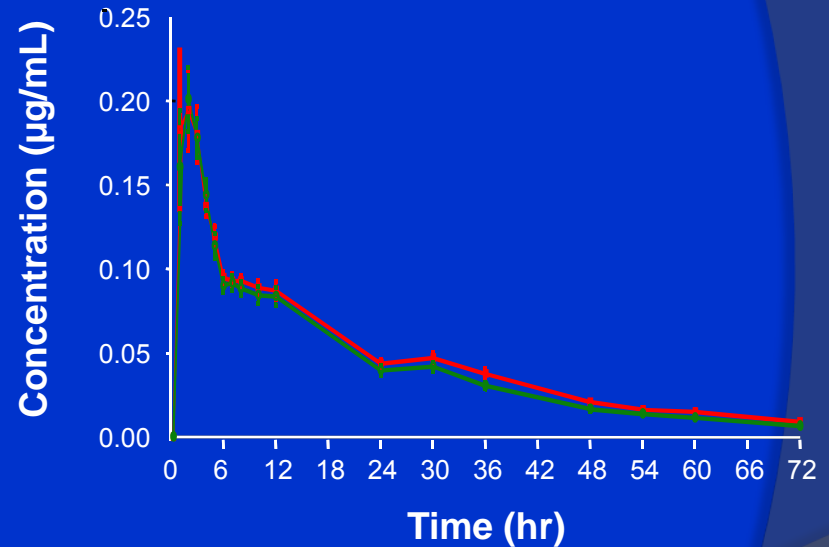
No Impact of RDEA806 on Emtricitabine or Tenofovir in Truvada

Time-Concentration Profiles in Plasma

Emtricitabine



Tenofovir



● Truvada only dosing

◆ Truvada and 800 mg QD RDEA806 x 4 days

No changes in RDE806 plasma levels observed when co-administered with Truvada or ritonavir

RDEA806 Conclusions

- Well tolerated with robust antiviral effect across all doses
- T_{max} ranged from 2-6 hours, half-life ~9-12 hours
- Antiviral activity similar between 800 mg QD and 400 mg BID
- No significant induction of CYP3A4, indicating a low potential for drug interactions
- Significant reduction in uric acid across all doses, with no effect on the renal excretion of tenofovir.
- Phase 2b in antiretroviral treatment-naïves planned to begin this quarter

Acknowledgements

Patients for their participation in the study

Chelsea and Westminster Hospital, London, UK

Marta Boffito, MD, Carl Fletcher, Ruth Bateson, Jessica Taylor

Institute for interdisciplinary Infectiology, Hamburg, Germany

Albrecht Stoehr, MD, Stefan Unger, MD, Nadine Emmerich, Nicole Bade

Medical University of Vienna, Vienna, Austria

Armin Rieger, MD, Veronique Touzeau-Römer, Bernd Gmeinhard

Ardea Biociences, Inc., San Diego, CA, USA

SGS Life Science Services, Belgium & USA