

Antiviral Activity of RDEA806, a Novel HIV Non-Nucleoside Reverse Transcriptase Inhibitor, in Treatment of Näive HIV Patients

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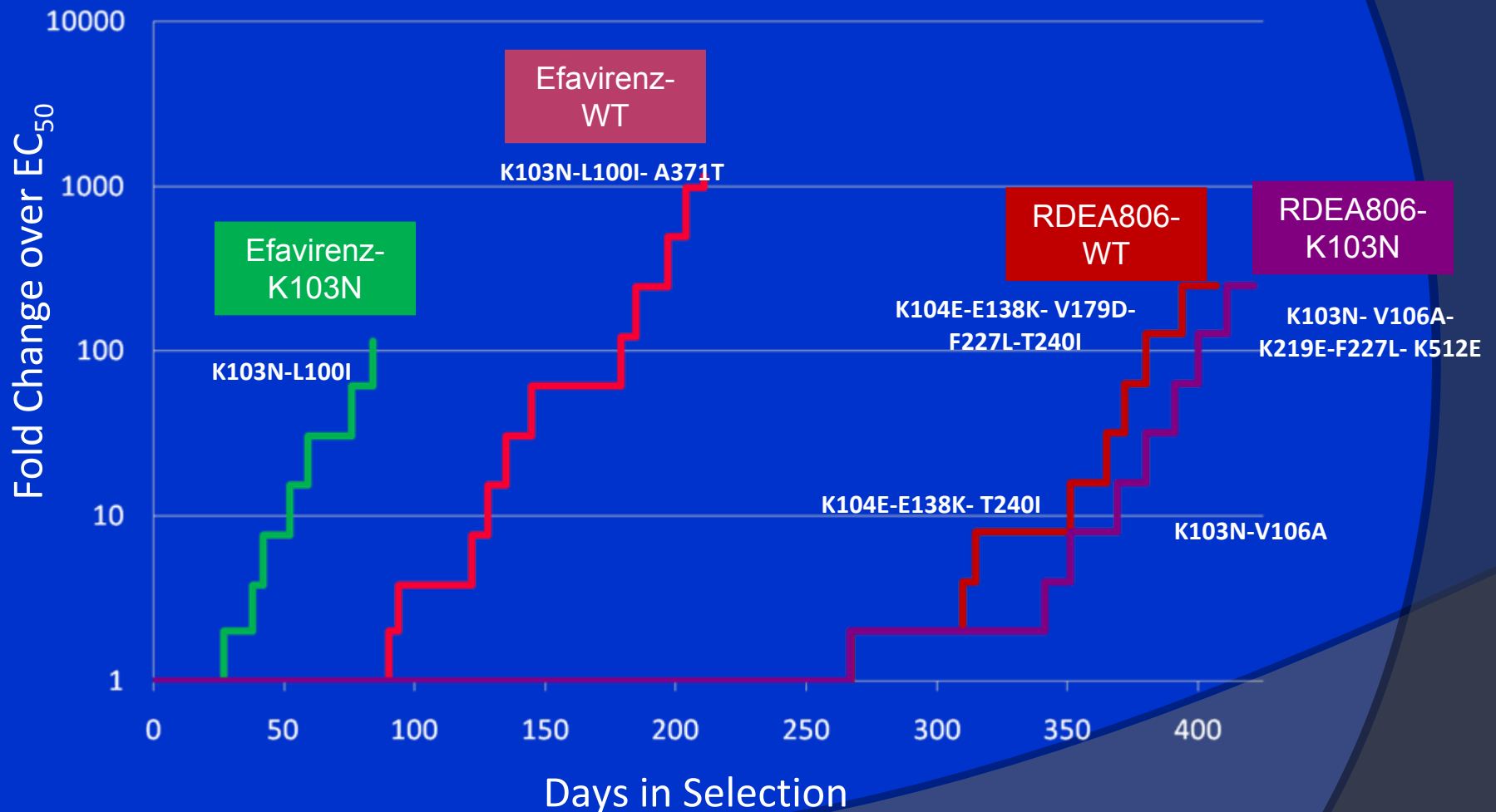
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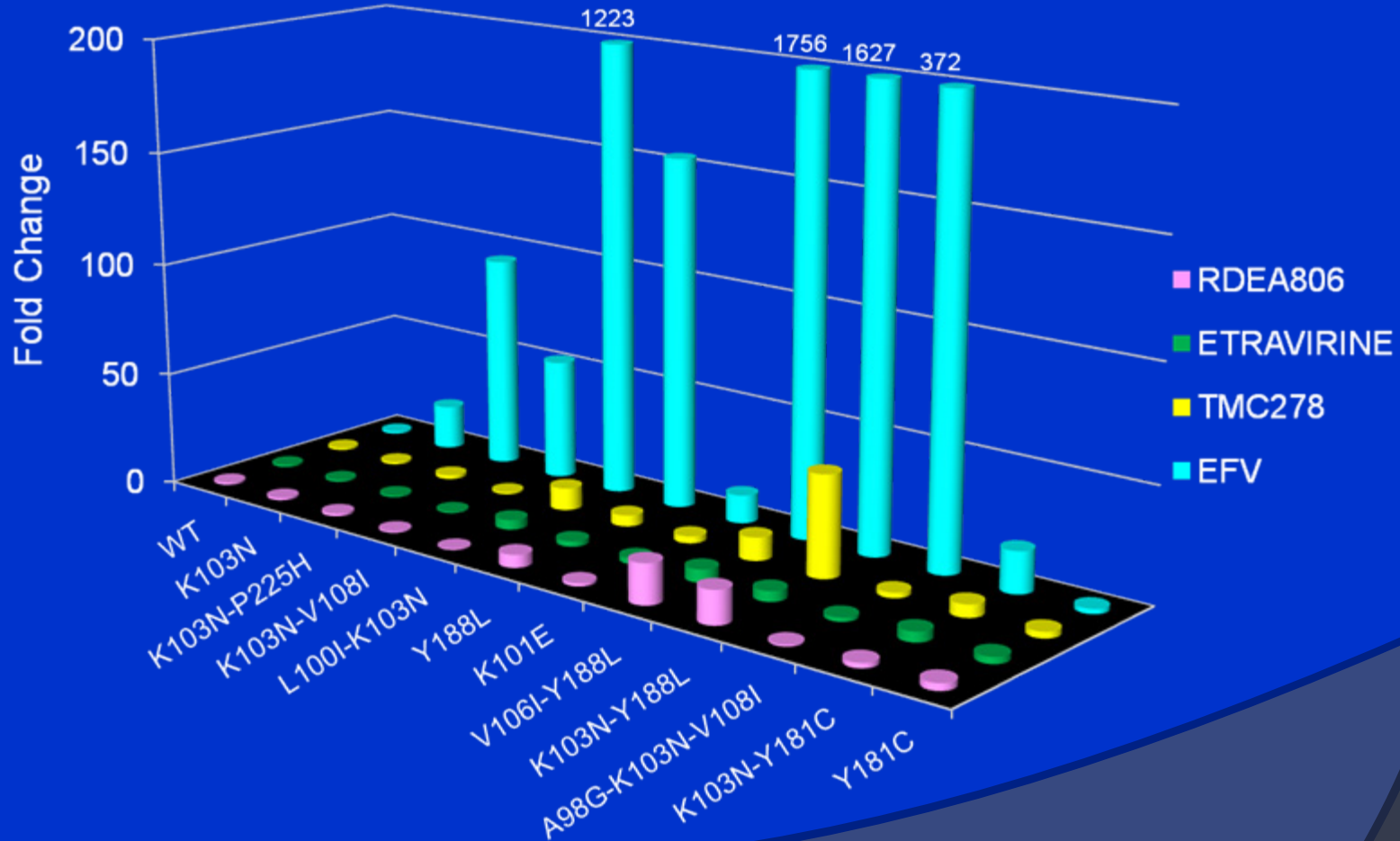
Preclinical Background

- RDEA806 is a potent, selective HIV NNRTI designed to maintain activity against the most common mutations observed with efavirenz
- High barrier to resistance
- Cytotoxicity selectivity index > 9,000
- Highly protein bound (~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

RDEA806 has Higher Barrier to Resistance



RDEA806 Activity In Vitro Against Common Resistant NNRTI-Resistant Viruses



Summary of Healthy Volunteer Data

- Safe and well tolerated by over 120 subjects at single doses up to 800 mg and multiple doses up to 1000 mg/day for 14 days
 - No evidence of CNS toxicity or drug related rash
- No significant trends in laboratory parameters except:
 - Statistically significant decreases in serum uric acid
 - Total cholesterol and triglycerides tended down
- Good oral bioavailability, linear PK, and terminal half-life of 11-13 hrs with multiple dosing
- Enteric-coated (EC) tablet formulation provides lower peak levels, improved trough plasma levels, and can be given without regard to food
- No significant interaction observed with ritonavir or with Truvada[®] (emtricitabine plus tenofovir)

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

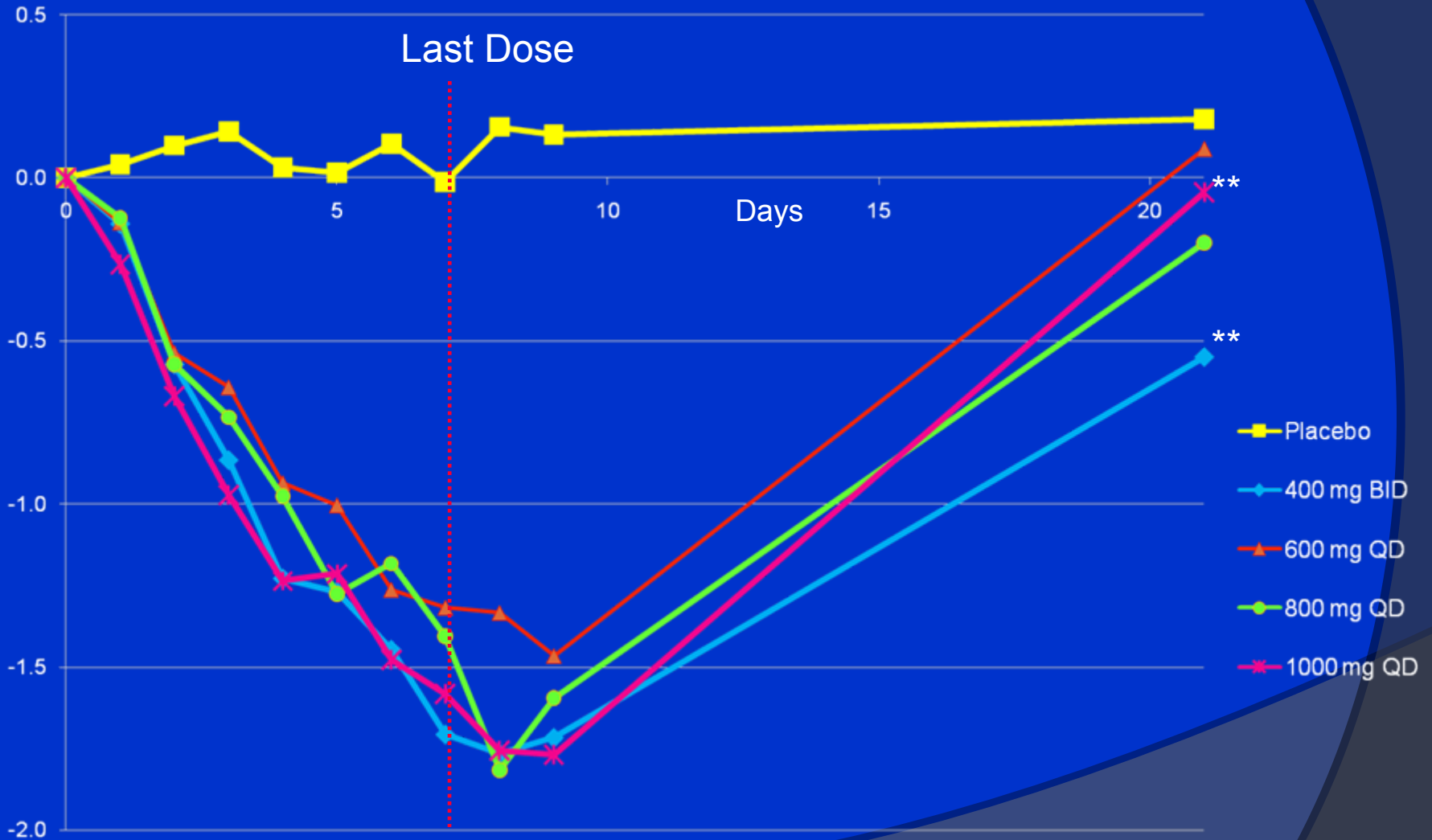
- Male patients
- 18-65 years
- Chronic HIV infection
- Antiretroviral treatment naïve or < 14 days prior therapy
- HIV RNA $\geq 5,000$ copies/mL
- CD4+ cell count
 - UK: ≥ 50 cells/mm³ for 2 cohorts, then ≥ 200 cells/mm³
 - Germany and Austria: ≥ 350 cells/mm³
- No history of AIDS-defining illness
- 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

**Some patients started on triple therapy prior to follow-up visit

Summary Viral Load Results

Median (IQR) Change (log ₁₀ copies/mL)	Day 8	Day 8 minus Placebo	Nadir*
Placebo	0.2 (-0.02; 0.03)		0.1
400 mg BID	-1.8 (-2.1; -1.7)	-1.9	-2.0
600 mg QD	-1.3 (-1.9; -1.0)	-1.5	-1.8
800 mg QD	-1.8 (-1.9; -1.2)	-2.0	-1.9
1000 mg QD	-1.8 (-1.8; -1.4)	-1.9	-1.8

Percent Patients	≥ 1 log Decrease	< 400 copies/ml
Placebo	0	0
400 mg BID	100%	56%
600 mg QD	78%	33%
800 mg QD	100%	67%
1000 mg QD	100%	44%

*Lowest value reached for each patient

Number of Patients Reporting Adverse Events of Moderate Severity or Greater

	RDEA806				PLACEBO
	400mg BID* N=9	600mg QD* N=9	800mg QD N=9	1000mg QD* N=9	All Active N=36
Back pain			1		1
Diarrhea				1	1
Headache		1	1		2
Insomnia			1		1
Pruritis	1				1

Adverse events are counted only one time per patient and only AEs that are at least possibly related to drug

* Dosed in fasted state

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

RDEA806 Conclusions

- Well tolerated with robust antiviral effect across all doses
- Antiviral activity similar between 800 mg QD and 400 mg BID
- No clinically important laboratory or ECG changes (no evidence of drug related QTc prolongation)
- Phase 2b in naïves planned with multiple QD doses

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