

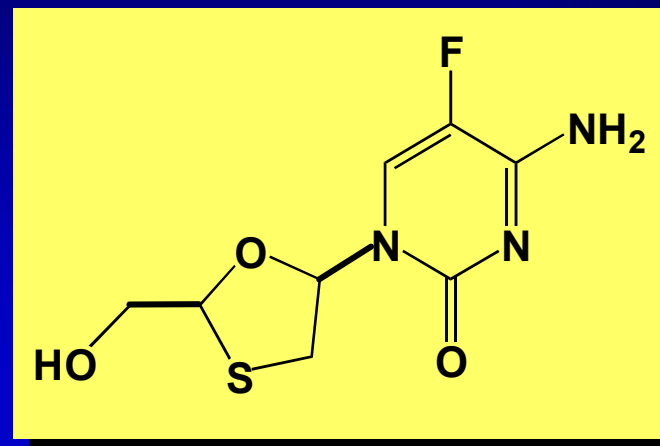
Racivir Demonstrates Activity in Patients Resistant to Lamivudine

Pedro Cahn¹, N. Sosa², A. Wiznia³, M. Patel³, D. Ward⁴, F. Palella⁵, J. Sierra-Madero⁶, D. Wheeler⁷, A. Burnside⁸, L. Bush⁹, E. DeJesus¹⁰, J. Jemsek¹¹

¹Fundación Huesped, Buenos Aires, Argentina, ²Medical Research Center, Panama City, Panama, ³Jacobi Medical Center, Bronx, New York, USA, ⁴Washington, DC, USA, ⁵Northwestern University, Chicago, IL, USA, ⁶Instituto Nacional de Nutrición Salvador Zubiran, Mexico City, Mexico, ⁷CARE-ID, Annandale, MD, USA, ⁸Burnside Clinic, Columbia, SC, USA, ⁹South Florida Clinical research, Atlantis, FL, USA, ¹⁰Orlando ImmunologyCenter, Orlando, FL, USA, ¹¹Jemsek Clinic, Huntersville, NC, USA.

Racivir

- Cytidine analog
- Chain terminator of HIV-RT
- In Phase II



Preclinical results:

- *In vitro* activity against wild type and certain resistant variants of HIV
- *In vitro* activity against HBV
- No safety issues in extended animal toxicology studies, including 12 months in dogs & 6 months in rats
- Potential benefit to delay the onset of drug resistance due to the M184V mutation

Phase I safety and PK study (RCV-100):

- Racivir was safe and well tolerated at all dose levels (0, 50, 100, 200, & 400 mg)
- Mean plasma levels remained above EC90 for wild type virus through 24 h
- One pill, once a day

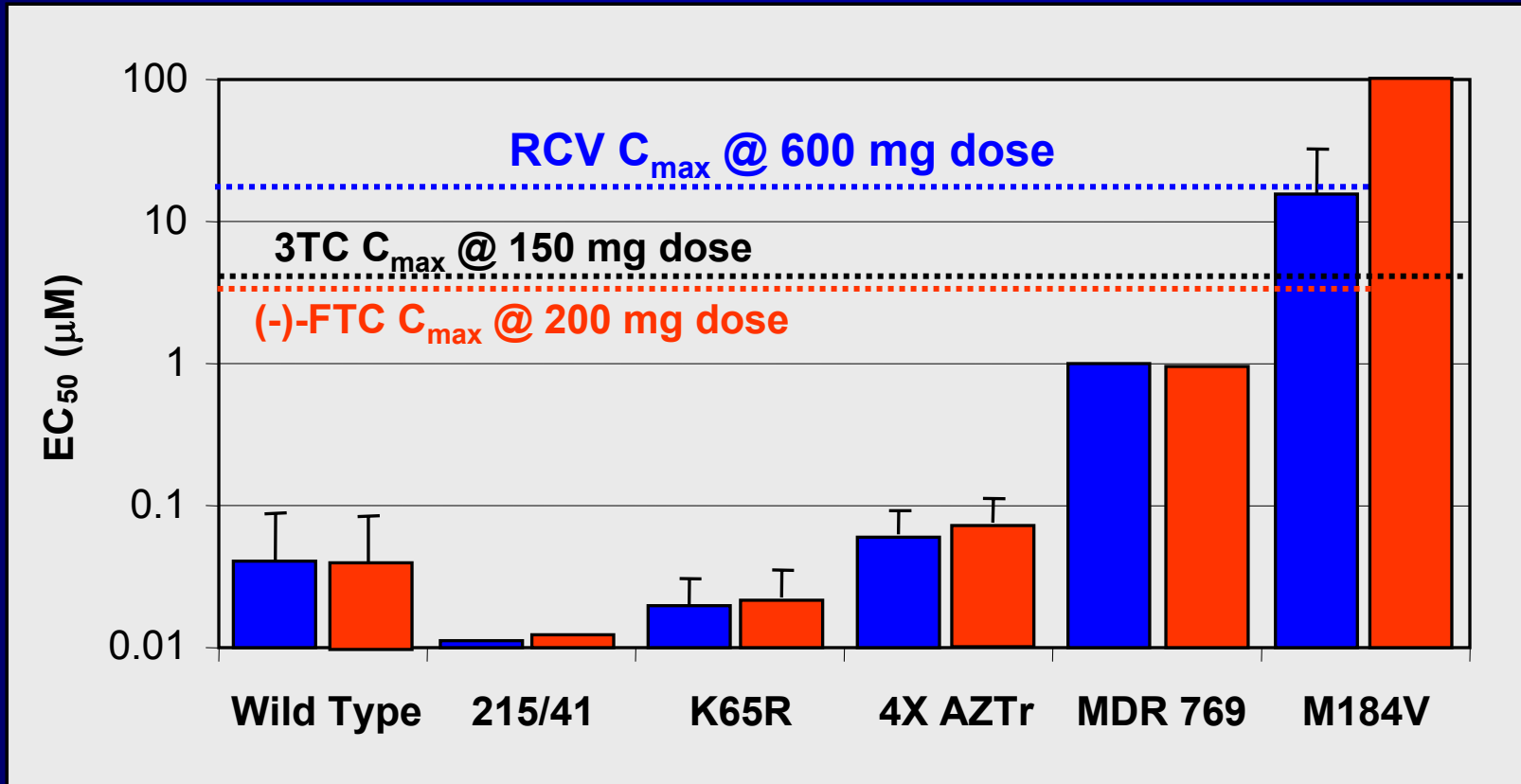
Racivir: A Racemic Mixture of FTC

	-FTC	+FTC
EC ₅₀	0.04 μM ± 0.14	0.55 μM ± 0.49
Cytotoxicity	>100 μM	>100 μM
Resistance	M184V	T215Y
Time to Resistance <i>In Vitro</i>	9 weeks	17 weeks

	Racivir (± FTC)
EC ₅₀	0.04 ± 0.06
Cytotoxicity	>100 μM
Resistance	M184V
Time to Resistance <i>In Vitro</i>	14 weeks

Schinazi et al., personal communication

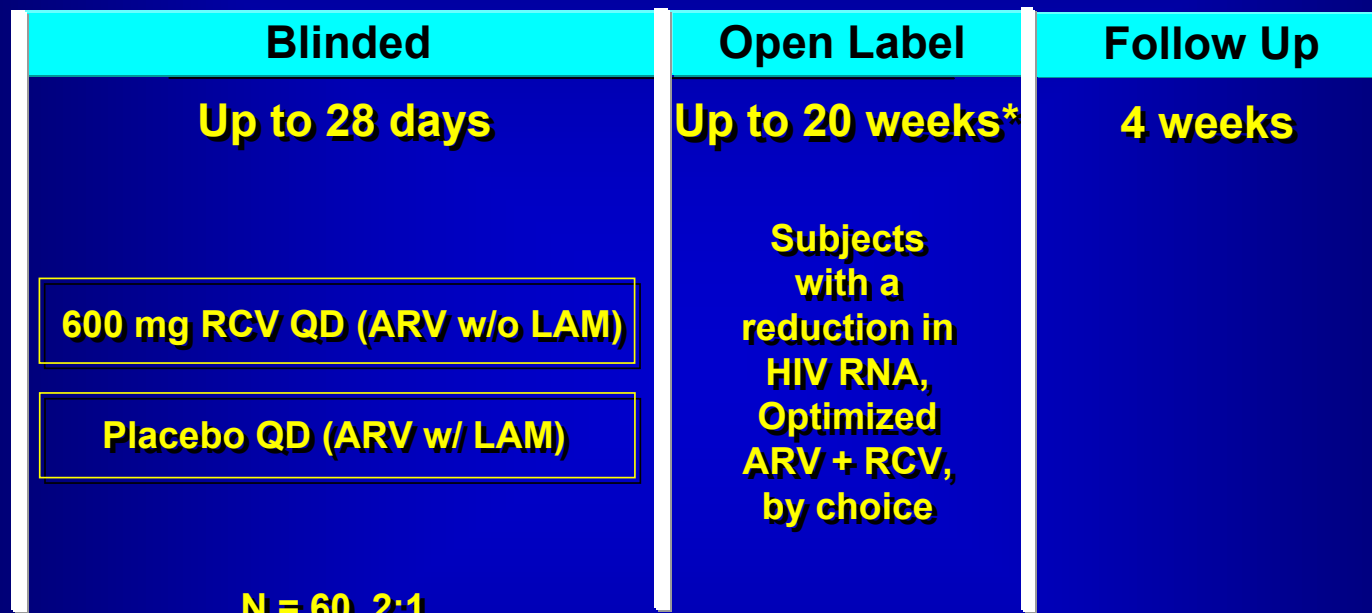
Racivir Achieves Blood Levels \geq EC₅₀ for M184V Mutant



MDR 769 : M41L, K65R, D67N, V75I, F116Y, Q151M, Y181I, L210W, T215Y

Sources: NIH Independent Testing; the Stanford Database

Racivir was tested against 3TC in patients with the M184V mutation



*or virologic failure – as defined by investigator

Entry Criteria: Stable LAM ARV, ≥ 60 days, M184V mutation, HIV RNA $\geq 2,000$ copies/mL, currently failing HAART therapy

Study 201 Inclusion Criteria

- Subjects currently on an accepted, stable HAART regimen that includes lamivudine for at least 60 days prior to screening.
- Subjects who have an HIV-RNA copy number of ≥ 2000 copies/mL (Amplicor HIV-1 Monitor® Test, v1.5)
- Subjects who have a CD4-lymphocyte count ≥ 50 cells/mm³.
- Subjects who have the M184V HIV mutation (Bayer TRUGENE® and OpenGene®).

Demographics

	Patients Receiving Racivir	Patient Receiving Placebo + 3TC
Number	35	16
% Male	83%	65%
% Female	17%	35%
Mean Age	44.7	42.3
Age Range	18.3 – 65.4	23.7 – 57.5
% Caucasian	40 %	47%
% Hispanic	31 %	35%
% Black	23%	18%
% Asian	3%	-
% Other	3%	-
Mean HIV VL	4.19 log ₁₀	4.07 log ₁₀
CD4 (Mean ± SD)	310 ± 158	323 ± 131

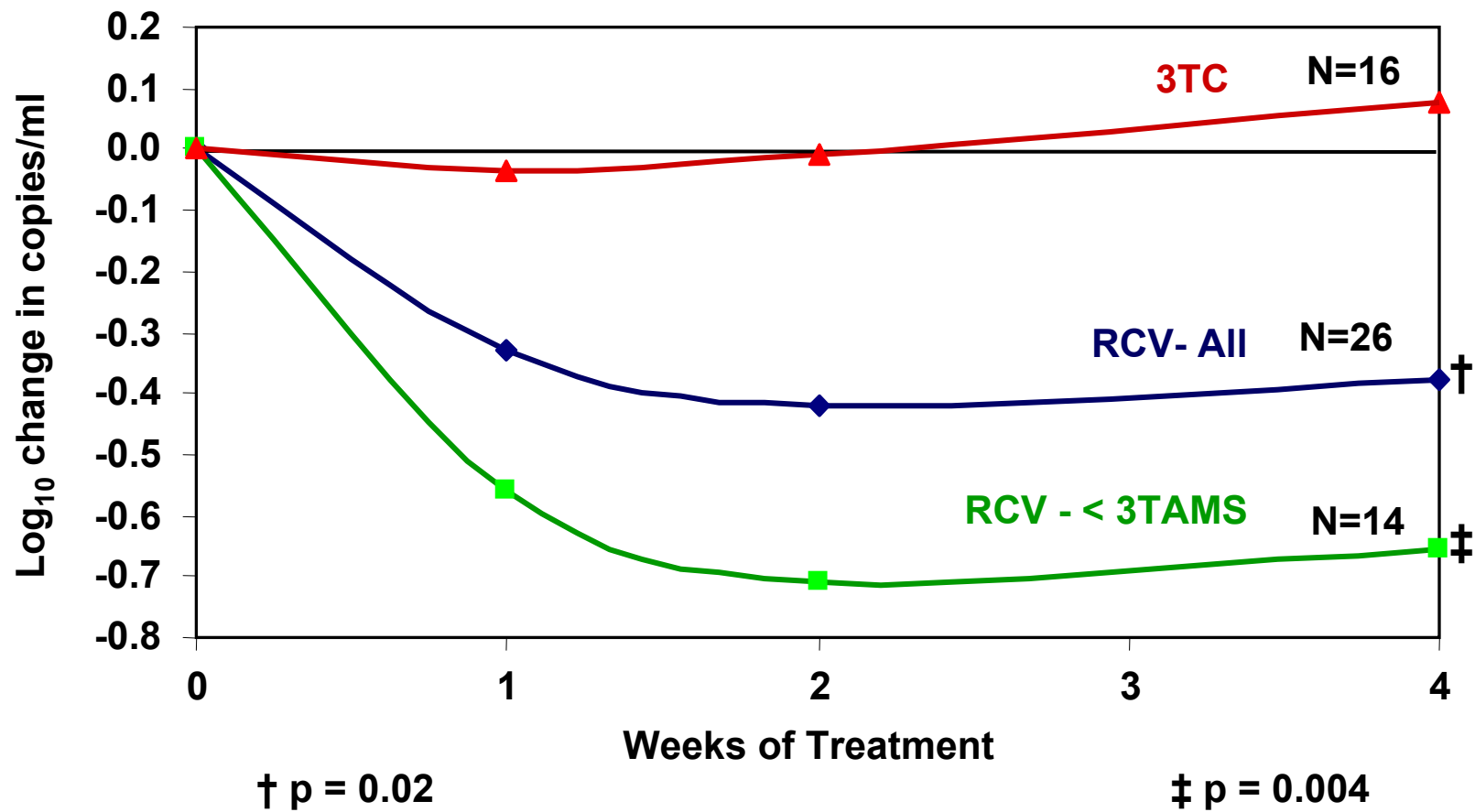
Listing of Adverse Events*

Adverse Event	% Patients Receiving RCV (n)	% Patients Receiving 3TC (n)
Headache	5.7 (2)	17.6 (3)
Dizziness	2.9 (1)	11.8 (2)
Somnolence	2.9 (1)	0
Abdominal Pain	2.9 (1)	0
Diarrhea	5.7 (2)	5.9 (1)
Nausea/ Vomiting	8.6 (3)	23.5 (4)
Decreased Appetite	2.9 (1)	0
Asthenia	2.9 (1)	0
Fatigue	5.7 (2)	5.9 (1)
Bronchitis	2.9 (1)	0
Folliculitis	0	5.9 (1)
Fungal Infection	0	5.9 (1)
Gastroenteritis	0	5.9 (1)
Sinusitis	0	5.9 (1)
Upper respiratory	5.7 (2)	11.8 (2)
Skin Disorders	11.4 (4)	5.9 (1)
Arthralgia/ Muscle pain	2.9 (1)	5.9 (1)
Elevated Serum Lipase	2.9 (1)	0
Proteinuria	2.9 (1)	0

*Adverse events were generally mild to moderate.

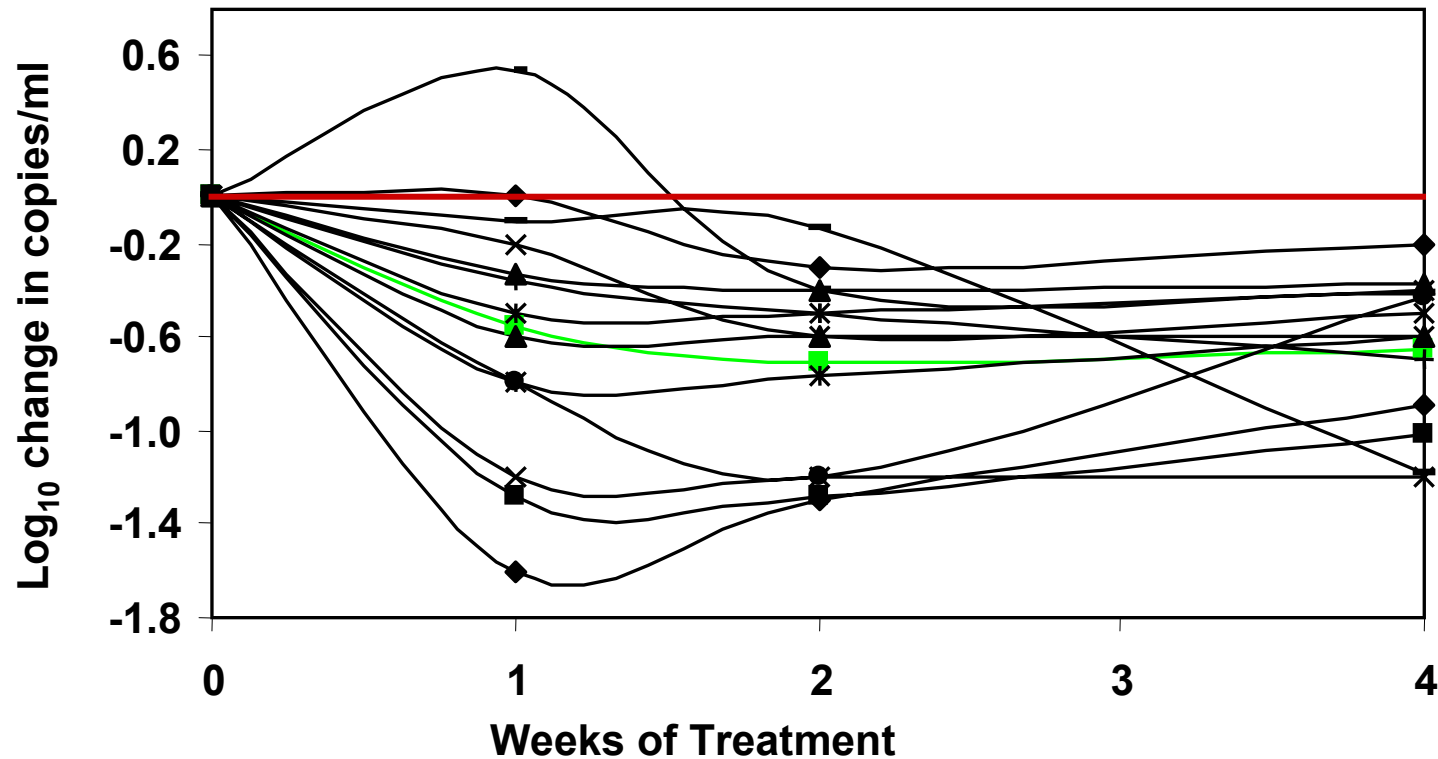
Preliminary Results from RCV 201 Study

RCV-201: Mean Change in HIV Viral Load



Preliminary Results from RCV 201 Study

RCV-201: Change in HIV Viral Load in Patients with M184V and < 3 TAMS



- Mean Change was $-0.7 \log_{10}$
- 28% Achieved undetectable viral load (<400 copies/ml)
- 64% had at least a $0.5 \log_{10}$ drop in viral load

Genotypes of Patients with < 3 TAMS Responding to Racivir

Genotypes	Log Drop
M184V, T215Y	-1.2 *
M184V	-1.2 *
M184V	-1.2
K103N, K108I, M184V	-1.1 *
K101Q, K103N, M184V	-0.9 *
A62V, Y181C, M184V, G190A	-0.7
V75I, K103N, M184V, P225H	-0.6
K103N, M184V	-0.5
K103N, M184V	-0.5
K104N, M184V	-0.4
M184V	-0.4
K103N, V108I, M184V, P225H	-0.4
K103N, M184V	-0.2
A63V, K101E/Q, M184V, G190S	-0.2

* Undetectable by PCR
(<400 copies/mL)

**These patients exhibit mutational patterns of first line failures
to 3TC/FTC, NNRTI's, AZT, and TDF**

Conclusions

- **Racivir demonstrated antiviral activity in treatment experienced patients**
 - **failing ARV therapy containing lamivudine and**
 - **harboring virus with the M184V and <3 TAMS**
- **Greatest efficacy seen in genotypes consistent with first line therapy failure**
- **Racivir has shown a potential to be considered a component of second line treatment regimens**
- **Future studies will explore this concept further**

Acknowledgements

- Michael Otto (Pharmasset)
- Abel De La Rosa (Pharmasset)
- Alejandro Krolewiecki (Fundacion Huesped)
- Lorena Abusamra (Fundacion Huesped)
- All the coinvestigators and patients.