

Antiretroviral Activity and Tolerability of Reverset (D-d4FC), a New Fluorocytidine Nucleoside Analog, When Used in Combination Therapy in Treatment-Experienced Patients: Results of Phase IIb Study RVT-203

C. Cohen,¹ C. Katlama,² R. Murphy,³ J. Gathe,⁴ C. Brinson,⁵ G. Richmond,⁶ P.-M. Girard,⁷ J. Fessel,⁸ A. Liappis,⁹ E. Puglia,¹⁰ B. Rodwick,¹¹ J. Nadler,¹² W. O'Brien,¹³ K. Arasteh,¹⁴ M. Otto,¹⁵ S. Erickson-Viitanen,¹⁶ and R. Levy¹⁶

¹Community Research Initiative of New England, Boston, USA; ²Hôpital de la Pitié, Paris, France; ³Northwestern University, Chicago, USA; ⁴Fannin Street, Houston, USA; ⁵Central Texas Clinical Research, Austin, USA; ⁶1315 SE 14th Street, Fort Lauderdale, USA; ⁷Hôpital St. Antoine, Paris, France; ⁸Kaiser Permanente, San Francisco, USA; ⁹George Washington University Medical Center, Washington, DC, USA; ¹⁰Research Center of Florida, Inc., Miami, USA; ¹¹Clinical Research of West Florida, Clearwater, USA; ¹²Hillsborough County Health Department, Tampa, USA; ¹³University of Texas Medical Branch, Galveston, USA; ¹⁴EPIMED, Berlin, Germany; ¹⁵Pharmasset, Inc. Tucker, USA; ¹⁶Incyte Corp., Wilmington, USA

ABSTRACT

Objectives: Evaluate efficacy and tolerability of once daily doses of 50, 100 or 200 mg Reverset (RVT), a cytidine analog NRTI, in ARV-experienced patients.

Methods: Phase IIb, randomized, blinded, multinational, placebo-controlled 3 stage study consisting of 2 wk add-on phase (RVT or placebo), 14-wk optimized treatment phase, and 8-wk safety phase (placebo pts allowed to cross over) in treatment-experienced patients (pts.).

Results: 199 pts enrolled at 25 sites; currently, 120 completed >16 wks of therapy. Mean baseline VL = 4.5 log₁₀, presence of M184V: 80%, M41L: 60%, 4-6 TAMs: 50%, K65R: 6%. After 2 wks, mean VL changed by +0.007, -0.5, -0.3, and -0.7 log₁₀ for placebo, 50, 100, and 200 mg groups respectively. Pts on 200 mg with 0-3 TAMs had 2-wk VL drop of 0.8 log₁₀, with 4-6 TAMs a 0.6 log₁₀ drop. Pts with M41L, M41L+L210W or w/o M41L showed similar VL decreases (0.7 log₁₀). Pts with K65R or M184V + TAMs had more variable responses (mean 0.4 log₁₀ drop); >20% pts had > 1 log₁₀ drop, 33% pts didn't optimize at wk 2. Of these, current data shows stable VL decrease of -0.5 log₁₀ at wk 16 on 200 mg RVT. AEs generally mild, included headache, fatigue and GI disorders. In 35 subjects taking RVT with ddi, 12 (34%) had grade 4 hyperlipaemia, usually occurring after >12 wks of treatment. Among pts not on ddi, asymptomatic grade 4 lipase seen in 5.4% of pts on 200 mg RVT vs. 3.1% on placebo. Pancreatitis seen in 3 pts on RVT+ddi+TDF: 1 pt on ddi 250mg/TDF 450mg, 1 pt on ddi 400mg/TDF 300mg; all resolved off drugs.

Conclusions: RVT 200 mg is active in ARV-experienced pts and generally well tolerated. Because of the risk of elevated lipase and pancreatitis, RVT should not be used with ddi. Data support continued development of RVT.

Background Information

- Preclinical studies demonstrated**
 - Active with viral mutants resistant to 3TC, TDF, AZT, other NRTIs, NNRTIs, and PIs
 - Long intracellular half-life (17 hours)
 - No mitochondrial toxicity or lactic acid increase (in vitro)
- 10-day add-on dosing demonstrated**
 - VL decrease of 0.8 logs with 200 mg qd dosing in therapy-experienced patients
 - VL decrease of 1.8 logs with 200 mg qd dosing in therapy-naïve patients

Chemical structure of REVERSE™ (D-d4FC): NC1=NC(=C(NC1=O)C(F)(F)F)C(F)(F)F

PO-2: Operon-273 (dimeric dimerization)

RVT-203 Study Design

Randomized, placebo-controlled, double-blind study in 3 phases:

- 2-week add-on:** 14-week treatment with optimized background regimen
- 8-week placebo cross-over:** 8-week placebo cross-over

- Determine short-term potency/select dose
- Assess impact of resistance mutations
- Assess impact of concurrent ARV
- Determine durability of response/select dose
- Assess development of resistance mutations
- Assess impact of optimized background
- Identify populations which will benefit most
- Assess longer term safety and tolerability

Baseline Characteristics

Parameter	Placebo (N=41)	50 mg (N=40)	100 mg (N=49)	200 mg (N=51)
Mean baseline VL, logs	4.52	4.25	4.40	4.59
No. with VL > 5 logs	4	7	11	14
No. who did not optimize at week 2	15	17	21	13
No. with 0-3 TAMs	25	28	27	29
No. with 4-6 TAMs	22	20	22	22
No. with both M41L and L210W	22 (47%)	20 (42%)	22 (45%)	25 (49%)
No. with M184V	31 (86%)	35 (73%)	30 (61%)	32 (63%)
No. with K65R	3	2	4	2

Demographics and Endpoints

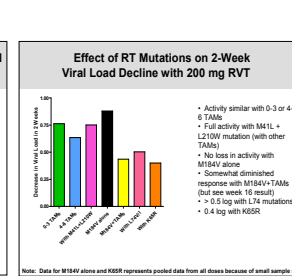
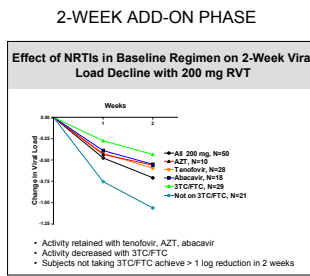
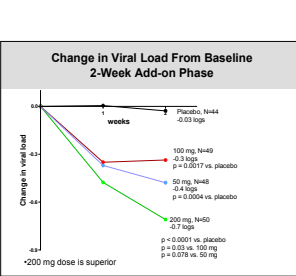
Parameter	N as of July 1, 2009
No. enrolled	199
No. completing week 16	171
No. completing week 24	112*
Percentage black or multi-racial	16.4%
Percentage female	8%

*Study is still ongoing

Endpoints

- Primary variables
 - Mean change in viral load to week 2 and week 16
 - Adverse events (AEs)
- Secondary variables include
 - Proportions > 1 log decline
 - Patients who did not optimize at week 2

RESULTS



WEEK 16 (2-WEEK ADD-ON PHASE PLUS 14-WEEK OPTIMIZATION PHASE)

Study RVT-203: 16-week Efficacy Results

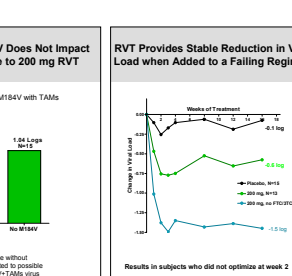
	Placebo (N=40)	RVT 50 mg (N=42)	RVT 100 mg (N=42)	RVT 200 mg (N=43)	200 mg vs Placebo
Decrease in VL (log ₁₀) from BL					
All	0.8	0.9	0.8	1.2	0.4
Non-optimizers	0.07	0.3	0.4	0.6	0.5
Responder Rate (VL > 1 log ₁₀ decrease in VL)					
All	40%	38%	31%	54%	14%
Non-optimizers	8%	0%	11%	31%	23%

* p < 0.0001 vs. placebo
p = 0.03 vs. 100 mg
p = 0.07 vs. 50 mg

Sub-Group Analysis

Sub-Group	Δ VL	% > 1 log Decrease		
Triple Class Failures N=7	-0.5	-0.9	25%	43%
No 3TC/FTC	-0.5	-1.4	25%*	80%*
All Subjects N=29	-0.3	-1.5	0%	86%

* p < 0.05



Number of Subjects with Possibly Related Clinical Adverse Events of Least Moderate Severity Through 16 Weeks

Event	Placebo (N=40)	RVT 50 mg (N=42)	RVT 100 mg (N=42)	RVT 200 mg (N=43)
Nausea	0	2	1	1
Headache	0	1	1	2
Dizziness	2	1	1	1
Pancreatitis	0	0	1	0
Hyperlipaemia	0	2	2	0
Asymptomatic Pan	0	0	1	0
Diarrhea	0	0	0	1
Dry Mouth	0	0	1	0
Fatigue	0	0	0	1
Abnormal Fatig	0	1	0	0
Blurred Vision	0	0	0	1
Constipation	0	0	0	1
Arthralgia	0	0	0	1
Blurred Vision	0	0	0	1
Diarrhea	0	0	0	1
Hyperlipaemia	0	0	1	0

Hyperlipaemia-Grade 4

Parameter	Placebo	50 mg	100 mg	200 mg
Patients <u>not</u> on ddi	1/39	1/37	2/34	2/37
	3%	3%	6%	5%
Patients <u>on</u> ddi	0/8	1/11	4/15	7/14
	0%	9%	27%	50%

- Low frequency of hyperlipaemia without ddi
- High frequency of hyperlipaemia with ddi
- 3 patients on 100 mg RVT had symptomatic pancreatitis
- RVT should not be used with ddi

Pancreatitis

4 Cases of pancreatitis, all on 100 mg RVT

- N=3 symptomatic pancreatitis**
 - One patient taking full dose (400 mg) ddi + tenofovir
 - One patient taking 250 mg ddi plus 1.5X dose tenofovir (450 mg)
 - One patient with ongoing alcohol abuse
- N=1 asymptomatic, radiographic pancreatitis**
 - Taking recommended doses of ddi + tenofovir
- All patients recovered**
 - Rapid, symptomatic and radiographic recovery
 - No complications
 - Lipase/amyase levels recovered more slowly

Other Possibly Related Serious Adverse Events in Subjects on RVT

- Anemia (1 patient on 200 mg RVT)
 - Also receiving AZT
- Neutropenia (1 patient on 200 mg RVT)
 - Worsening neutropenia when started on TMP-SMX for PCP
- Hypertriglyceridemia (1 patient on 100 mg RVT)
 - Developed worsening hypertriglyceridemia when started on fosamprenavir 1400 mg and ritonavir 200 mg once daily
- Pancytopenia (1 patient on 200 mg RVT)
 - Developed anemia (Grade 3), neutropenia (grade 3) and thrombocytopenia (Grade 2), resolved with discontinuation of study medication
 - No other evidence of bone marrow toxicity in the entire study

CONCLUSIONS

- 200 mg Reverset provides antiviral suppression in highly ARV-experienced patients
 - 2-week add-on phase: -0.7 logs
 - 1.1 log₁₀ without 3TC/FTC
 - 16 weeks: 54% response overall (> 1.0 logs)
 - 80% without 3TC/FTC
- Reverset is generally well tolerated
 - Asymptomatic hyperlipaemia when used with ddi
 - RVT should not be used with ddi
- Reverset activity retained with key mutations
 - To date, no novel mutations identified in RVT-exposed patients
 - No K65R emerged to date in RVT-exposed patients
- Reverset warrants further development
 - Phase III trial planning in progress

ACKNOWLEDGMENTS

Participating subjects

Investigators

United States: Calvin Cohen, Joseph Gathe, Jeffrey Fessel, Angelle Lippis, Barry Rodwick, William O'Brien, Jeffrey Galpin, Donna Miskov, Corkin Steinhart

France: Rob Murphy, Cynthia Brinson, Gary Richmond, Edgardo Puglia, Jeffrey Nadler, Steven O'Maro, George Beatty, Kathleen Swartz, Gerald Plenne

Germany: Kolosova Arasteh, Dirk Schurmann, Shimo Staszewski, Hans-Jürgen Stellbrink, Albrecht Stehr

Sponsors

Incyte Corporation, Pharmasset, Inc.