Poster
LB-8

Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Co-infected Patients: A 24-Week Treatment Interim Analysis

KE Sherman[1], JK Rockstroh[2], DT Dieterich[3], V Soriano[4], PM Girard[5], S McCallister[6], N Adda[6], M Bsharat[6], BS Adiwijaya[6], L Mahnke[6], MS Sulkowski[7]

[1]University of Cincinnati College of Medicine, Cincinnati, OH, United States; [2]University of Bonn, Bonn, Germany; [3]Mount Sinai School of Medicine, New York, NY, United States [4]Hospital Carlos III, Madrid, Spain; [5]Hôpital St Antoine, Paris, France; [6]Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States; [7]Johns Hopkins University School of Medicine, Baltimore, MD, United States.

*Address correspondence to:
Kenneth E. Sherman, MD, PhD.
Division of Digestive Diseases, University of Cincinnati College of Medicine, Cincinnati, OH
Email: shermake@ucmail.uc.edu

BACKGROUND

- INCIVEK (telaprevir, TVR) is an inhibitor of the hepatitis C virus (HCV) protease NS3/4A whose use in combination with pegylated interferon-alfa-2a (P) and ribavirin (R) was recently approved by the Food and Drug Administration (FDA) for the treatment of chronic genotype 1 HCV mono-infected patients in the US, Europe, and Canada.[1-3]
- In genotype 1 mono-infected patients, telaprevir with peginterferon alfa-2a/ribavirin (T/PR) led to substantial improvements in SVR in phase 3 studies[1,4-6]:
  - Treatment-naïve patients (ADVANCE trial, N=1088),[4]
    - 79% vs 46% in patients treated with 12-week telaprevir combination treatment vs peginterferon/ribavirin alone
  - Treatment-experienced patients (REALIZE trial, N=662)[6]:
    - 32% vs 5% in control (prior null responders)
    - 59% vs 15% in control (prior partial responders)
    - 86% vs 22% in control (prior relapsers)
- Modest DDI between TVR and ART (EFV, ATV/r and TDF) was observed, no dose adjustment for ART was deemed necessary[7]
- Higher TVR dose (1125 mg q8h) could partly offset TVR interactions with EFV[7], no other TVR dose adjustment was deemed necessary

METHODS

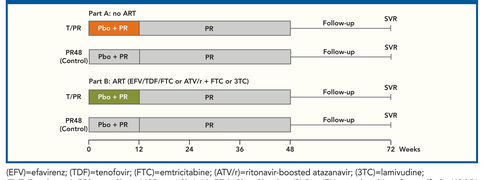
STUDY OBJECTIVES

Primary Objectives:
- To assess the safety and tolerability of telaprevir, peginterferon, and ribavirin in chronic HCV genotype 1/HIV co-infected patients
- To evaluate the proportion of patients with HCV RNA undetectable after a total of 24 weeks treatment with telaprevir, peginterferon, and ribavirin

Secondary Objectives:
- To evaluate the efficacy of telaprevir combination treatment 24 weeks after last dose (SVR)
- To assess the pharmacokinetics of telaprevir, peginterferon and ribavirin
- To analyze the selection of HCV resistant variants
- In Part B only, to assess the pharmacokinetics of pre-specified ART medications

Principal Eligibility Criteria
- Male and female patients, 18 to 65 years of age with chronic HCV genotype 1/HIV 1 co-infection, and treatment-naïve for HCV
- Liver biopsy within 1 year; compensated cirrhosis permitted
- Part A: up to 20 patients not receiving ART, with CD4 count ≥500 cells/mm^3, and HIV RNA ≤100,000 copies/mL
- Part B: up to 48 patients receiving a stable ART regimen
  - EFV/TDF/FTC, or
  - ATV/r with TDF and FTC or 3TC, with CD4 count ≥300 cells/mm^3, and HIV RNA ≤50 copies/mL

Figure 1: Study 110 Design



(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine; (T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R) RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany). Roche COBAS TaqMan HCV test v2.0, LLOQ of 25 IU/mL, LOD of <10 IU/mL

- There were 5 patients in Part B who had weight-based ribavirin per country requirements (France and Germany). All patients in Part B received FTC.

ASSESSMENTS

- HIV RNA Day 1, Week 4, 8, 12, 24, 36, 48, and at safety follow-up (4 weeks after last dose of study drug)
- CD4: Day 1, (Week 4 and 8 for Part B), Week 12, 24, 36, 48, and at safety follow-up (4 weeks after last dose of study drug)
- HCV RNA: Day 1 (1 predose, 2 postdose), 2, 4, and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 36, 48 during TVR/Pbo during and at follow-up.
- Proportion of patients with undetectable HCV RNA undetectable at Weeks 4, 12, Weeks 4 and 12, and Week 24
- Pharmacokinetic assessments were as follows: For telaprevir, samples were taken at the following timepoints: Days 1 (1 predose, 6 postdose), 8, 15, 29 (1 predose, 6 postdose), and 85. For pre-specified ART medications, Days -1, 1, 8, 15, 29, and 85.

PREDEFINED STOPPING RULES

- Viral breakthrough (in all patients), defined as HCV RNA >100 IU/mL after HCV RNA undetectable or a 1 $\log_{10}$ increase from nadir at Week 4, 8, and 12, patients to discontinue all study drugs
- At Week 4 and 8, if HCV RNA >1000 IU/mL, T/PR patients to discontinue telaprevir, continue PR. At Week 12, if HCV RNA >1000 IU/mL in T/PR patients with ≥ 1000 IU/mL at Weeks 4 and 8, patients to discontinue all study drugs. In all other patients, if HCV RNA <2 $\log_{10}$ decline, patients to discontinue all study drugs. At Weeks 24 and 36, in all patients, if HCV RNA detectable, patients to discontinue all study drugs.

PATIENT POPULATION

- Interim analysis based on 60 patients receiving at least one dose of study drug out of 62 enrolled patients; 44/60 patients had reached Week 24 on study drug at time of analysis. Thirteen patients were in Part A. Forty-seven patients from Part B: 24 patients (EFV/TDF/FTC), 23 patients (ATV/r/TDF/FTC or 3TC)
- Among 16 patients that did not reach Week 24 on study drug: 6 met a stopping rule (Table 2), 1 was lost to follow-up, 1 discontinued due to a serious adverse event of hemolytic anemia, 2 withdrew consent, and 6 patients did not reach Week 24 on study drug for other reasons.

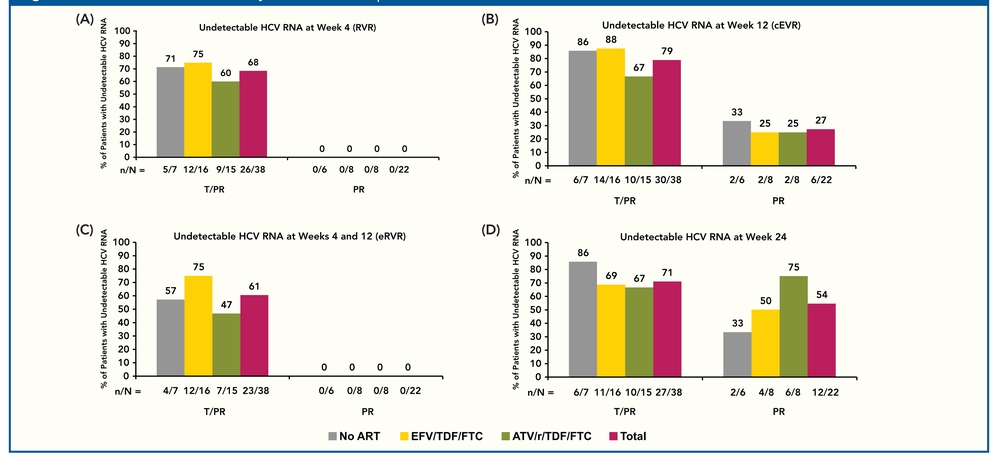
RESULTS

Table 1: Demographics and Baseline Characteristics

	Part A No ART		Part B EFV/TDF/FTC		Part B ATV/r + TDF + FTC/3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=15	PR N=8
Gender, n (%): Male	6 (86)	4 (67)	16 (100)	7 (87)	13 (87)	7 (87)
Caucasian†, n(%)	2 (29)	3 (50)	12 (75)	5 (62)	13 (87)	7 (87)
Black/African American, n(%)	4 (57)	3 (50)	3 (19)	3 (37)	2 (13)	1 (12)
Ethnicity†: Hispanic, n (%)	3 (43)	2 (33)	5 (31)	1 (12)	3 (20)	3 (37)
Age, median years (range)	39 (34-51)	48 (43-65)	48 (31-57)	47 (31-53)	52 (37-60)	39 (26-53)
BMI, median kg/m^2 (range)	29 (22-37)	31 (26-37)	24 (21-32)	23 (19-29)	24 (23-33)	25 (22-30)
HCV RNA ≥800,000 IU/mL**, n (%)	7 (100)	5 (83)	13 (81)	7 (88)	12 (80)	7 (88)
HCV Subtype 1a*, n (%)	3 (43)	3 (50)	12 (75)	6 (75)	12 (80)	5 (62)
HCV Subtype 1b*, n (%)	4 (57)	2 (33)	4 (25)	1 (12)	3 (20)	3 (38)
Bridging Fibrosis, n (%)	1 (14)	0 (0)	2 (12)	1 (12)	0 (0)	1 (13)
Cirrhosis, n (%)	0 (0)	0 (0)	2 (12)	0 (0)	0 (0)	0 (0)
HIV RNA median copies/mL (range)	1495 (155-53,450)	267 (50-21,950)	25	25	25	25
CD4+ median cells/µL (range)	604 (496-759)	672 (518-1189)	533 (299-1075)	514 (323-1034)	514 (279-874)	535 (302-772)

† Race and ethnicity were self-reported * 5'NC InnoLipa line probe assay ** Roche COBAS TaqMan HCV test v2.0, LLOQ of 25 IU/mL and LLOD of 10 IU/mL

Figure 2: Undetectable HCV RNA by Treatment Group



VIROLOGIC BREAKTHROUGH AND FAILURE

- There were no HIV RNA breakthroughs
- 7 T/PR patients experienced HCV RNA breakthrough:
  - 1 receiving EFV/TDF/FTC and 1 receiving ATV/r + TDF/FTC at Week 4
  - 1 receiving EFV/TDF/FTC and 1 receiving ATV/r + TDF/FTC at Week 8
  - 2 receiving EFV/TDF/FTC and 1 receiving ATV/r + TDF/FTC at Week 12

Table 3: Discontinuation from Study Drug Due to Stopping Rules

	Part A No ART		Part B EFV/TDF/FTC		Part B ATV/r + TDF + FTC/3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=15	PR N=8
Week 4	0	0	0	0	1 (7)	0
Week 8	0	0	1 (6)	0	0	0
Week 12	0	2 (33)	0	1 (12)	0	1 (12)
Week 24	0	2 (33)	0	0	0	1 (12)

SAFETY RESULTS

Table 3: Most Common Adverse Events*

%	T/PR (N=38)	PR (N=22)
Fatigue	42	41
Pruritus	**40**	**9**
Headache	**37**	**27**
Nausea	**34**	**23**
Diarrhea	24	18
Dizziness	**21**	**9**
Pyrexia	**21**	**9**
Depression	**21**	**9**
Neutropenia	21	23
Anorexia	10	4
Vomiting	18	9
Myalgia	16	23
Chills	16	18
Weight Decreased	10	23
Insomnia	13	23

*Reported in >15% of patients regardless of severity in any treatment arm, in bold event occurring at >10% points in any T/PR group vs PR. Abdominal pain occurred more frequently in the T/PR groups (≥10% difference) compared to PR as well.

PHARMACOKINETIC RESULTS

Table 5: Comparison of Telaprevir Steady-state Concentration by ART Regimens

Parameter	ART Drug Regimens	In HIV/HCV Co-infected Patients: Ref conc (no ART) Mean (ng/mL)	Conc Ratio to Ref (%) Mean	90% CI LB	90% CI UB	In Healthy Volunteers: Ref conc (no ART) Mean (ng/mL)	Conc Ratio to Ref (%) Mean	90% CI LB	90% CI UB
C_{min}	EFV	1984	93	56	156	1640	75	66	87
C_{min}	ATV/r	1984	131	77	222	1840	85	75	98
C_{avg}	EFV	2830	97	64	146	2299	82	73	92
C_{avg}	ATV/r	2830	107	70	165	2553	80	76	85
C_{max}	EFV	3718	101	72	143	2985	86	76	97
C_{max}	ATV/r	3718	98	69	140	3316	79	74	84

EFV= efavirenz-based ART regimen ATV/r= atazanavir/ritonavir-based ART regimen

- No severe rashes were reported.
- Four patients (1 Part A and 2 Part B) received an erythropoietin stimulating agent.
- 12 T/PR and 5 PR patients had Grade 3 hemoglobin levels
- CD4 counts declined in both T/PR and PR groups; CD4% remain unchanged.
- Bilirubin adverse events occurred more frequently in 27% (4/15) of ATV/r patients receiving T/PR compared to 0% (0/8) in ATV/r patients receiving PR alone as did indirect bilirubinemia.
- Patients in the T/PR group had lower baseline indirect bilirubin levels (13 µmol/L [95% CI 2, 55]) and experienced a higher change from baseline at Week 1 (mean 29 µmol/L [95% CI 2, 175]) compared to the control arm (baseline mean: 18 µmol/L [95% CI 1, 75]; Week 1 mean 22 µmol/L [95% CI 2, 169]). At Week 12 mean indirect bilirubin levels were 18 µmol/L [95% CI 2, 87]) and 18 µmol/L [95% CI 2, 169]) in T/PR and PR, respectively.
- One patient in the T/PR ATV/r-based group discontinued telaprevir at Week 3 due to a severe AE of jaundice (Table 5).

Table 4: Adverse Events and Treatment Discontinuation

	Part A No ART		Part B EFV/TDF/FTC		Part B ATV/r + TDF + FTC/3TC	
	T/PR N=7	PR N=6	T/PR N=16	PR N=8	T/PR N=15	PR N=8
Any AE, n (%)	7 (100)	6 (100)	16 (100)	8 (100)	15 (100)	8 (100)
Serious AE*†, n (%)	1 (14)	0	1 (6)	0	5 (33)	1 (12)
Discontinuation of all study drugs due to AE, n (%)	0	0	0	0	2 (13)	0
Due to jaundice	0	0	0	0	1 (6.7)	0
Due to cholelithiasis	0	0	0	0	1 (6.7)	0
Due to hemolytic anemia*	0	0	0	0	1 (6.7)	0

*Hemolytic anemia was reported as a serious adverse event.
† One additional patient had a serious AE of pneumococcal pneumonia reported after the Week 4 safety follow-up visit.

- Patients receiving the ATV/r-based regimens in both the T/PR and control arms experienced elevated indirect bilirubin upon HCV treatment. The elevated bilirubin was related to atazanavir exposure, consistent with previously reported literature.[8]

Table 6: Pharmacokinetics of ART After and Before HCV Treatment in HIV/HCV Co-infected Patients and in Healthy Volunteers

ART Medication	In HIV/HCV Co-infected Patients: Median Cmin before HCV treatment (ng/mL) +TVR/PR	+PBO/PR	Median (10th - 90th percentiles) ratio of C_{min} before and after HCV treatment* +TVR/PR	+PBO/PR	Reference C_{min}, AUC, C_{max} of ART C_{min}	C_{avg}	C_{max}	In Healthy Volunteers: Mean (90%CI) conc ratio of ART C_{min}, AUC, C_{max} relative to reference C_{min}	C_{avg}	C_{max}
Atazanavir (ATV)	1230	1890	122% (54% - Undef)	81% (16% - 220%)	805	1981	5169	185% (140% - 244%)	117% (97%-142%)	85% (73% - 98%)
Efavirenz (EFV)	1441	1925	86% (53% - 165%)	66% (52% - 148%)	1955	2897	5287	90% (81%-101%)	82% (74% - 90%)	76% (68% - 85%)
Tenofovir (+EFV)	61.2	67.6	90% (60% - 422%)	59% (42% - 201%)	51.3	113.8	343.5	117% (106%-128%)	110% (103% - 118%)	122% (112%-133%)
Tenofovir (-EFV)	128.1	139	83% (35% - 353%)	74% (53% - 170%)	52.8	123.0	312.1	141% (129% - 154%)	130% (122%- 139%)	130% (116%-145%)

EFV= efavirenz-based ART regimen ATV= atazanavir/ritonavir-based ART regimen

- Week 4 intensive telaprevir pharmacokinetic data were comparable across ART regimens, and also comparable to the values in healthy volunteers (Table 4).
- Pharmacokinetics of ART medications when co-administered with T/PR resulted in modest changes that are consistent with the values obtained in DDI studies in healthy volunteers as shown in Table 5.

CONCLUSIONS

- **In this interim analysis, higher Week 24 on-treatment responses were seen in chronic genotype 1 HCV/HIV co-infected patients treated with T/PR (74%) compared to PR alone (54%).**
- **TVR exposures were comparable across ART regimens. Higher TVR dose (1125 mg q8h) with EFV resulted in TVR exposures that were comparable to other ART groups thus, no other TVR dose adjustment was deemed necessary. Modest interactions were observed between TVR and ART; no dose adjustment in ART medication was deemed necessary.**
- **Bilirubinemia was notable in patients receiving T/PR with an ATV/r-based regimen. Overall safety and tolerability of patients treated with TVR combination treatment was comparable to that previously observed in chronic genotype 1 HCV-monoinfected patients.**

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AUTHOR DISCLOSURES

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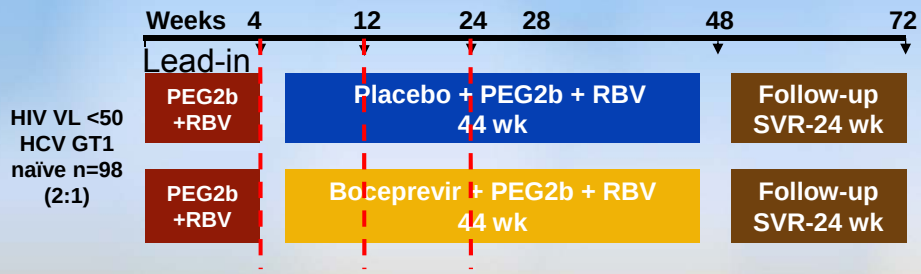
Boceprevir Plus Peginterferon/Ribavirin for the Treatment of HCV/HIV Co-Infected Patients

M Sulkowski, S Pol, C Cooper, H Fainboim, J Slim, A Rivero, S Thompson, W Greaves, J Wahl, J Mallolas

BOC + PEG/RBV for HCV/HIV Co-Infection (interim analysis)

Phase II, BOC-double-blinded 800mg TID, PEG2b 1.5µg/kg QW/RBV WB



- >90% pts reached W12 or 24 or had DC at the time of analysis
- Futility rules: W12: <2 log10 decline; W24: HCV RNA > LLOQ
- BL characteristics were well balanced, but cirrhosis: 1-control, 4-BOC

Sulkowski M et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. LB-37.

Use of Antiretroviral Therapy

	PR	B/PR
Any*	34 (100)	64 (100)
HIV Protease Inhibitors†	31 (91)	54 (84)
ATV/r	13 (38)	20 (31)
Lopinavir/r	10 (29)	16 (25)
Darunavir/r	7 (21)	12 (19)
NRTIs††	33 (97)	60 (94)
Integrase Inhibitors	4 (12)	11 (17)
CCR5 antagonists	1 (3)	1 (2)

* To maintain blinding in this continuing study, data is only shown where at least 1 patient in each treatment group is represented.
† HIV PIs included ATVr, DRV/r, LPV/r, fAMP/r, SAQ/r
† † NRTIs included TDF, ABC, 3TC, FTC

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Patient Disposition

	PEG2b/RBV	PEG2b/RBV + BOC
Treated, n (Percentage)	34 (100%)	64 (100%)
Discontinued during treatment phase, n (Percentage)	14 (41%)	16 (25%)
Due to AE, n (Percentage)	3 (9%)	9 (14%)
Due to treatment failure, n (Percentage)	11 (32%)	3 (5%)
Other reasons	0	4 (6%)
Completed treatment phase, n (Percentage)	1 (3%)	2 (3%)
Ongoing, n (Percentage)	19 (56%)	46 (72%)

Most commons AE > 10% Neutropenia, dysgeusia, vomiting, pyrexia, loss of appetite

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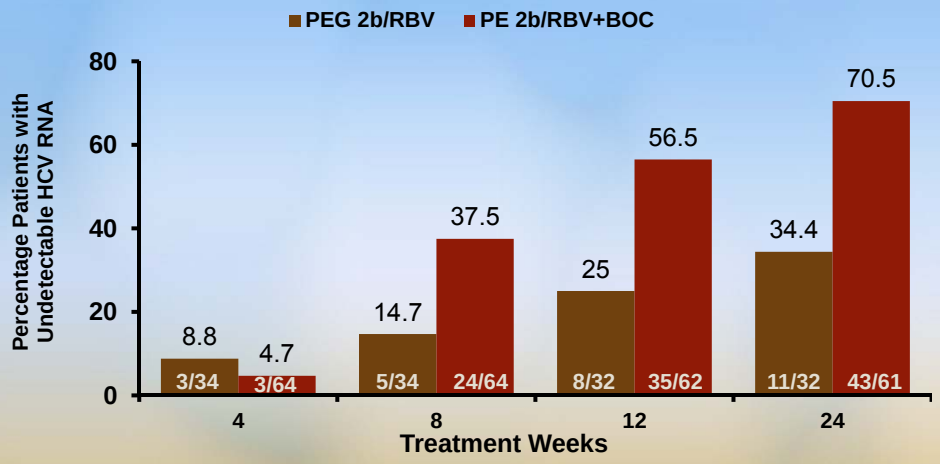
Virologic Response Over Time (% HCV RNA Undetectable)



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Most Common Adverse Events With a Difference of ≥10% Between Groups*

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (N=64)
Days on study, median	166	211
Neutropenia, (%)	3%	13%
Dysgeusia, (%)	15%	25%
Vomiting, (%)	15%	25%
Pyrexia, (%)	21%	34%
Headache, (%)	12%	28%
Decreased Appetite, (%)	18%	30%

*A difference of ≥10% for patients receiving PEG2b/RBV+BOC when compared with PEG2b/RBV.

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Hematologic Adverse Events

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (n=64)
Anemia		
AEs, n (%)	9 (26)	19 (30)
SAEs, n (%)	2 (6)	1 (2)
AEs leading to discontinuation, n (%)	1 (3)	1 (2)
Grade 2 (8.0 to <9.5 g/dL), n (%)	7 (21)	10 (16)
Grade 3 (6.5 to <8.0 g/dL), n (%)	1 (3)	3 (5)
Erythropoietin use, n (%)	7 (21)	17 (27)
Transfusions, n (%)	2 (6)	4 (6)
Neutropenia		
AEs, n (%)	1 (3)	8 (13)
Grade 3 (<0.75x10^9/L), n (%)	3 (9)	10 (16)
Grade 4 (<0.5x10^9/L), n (%)	*	*

*To maintain blinding in this continuing study the table only shows data where events occurred in at least 1 patient in each treatment group.

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