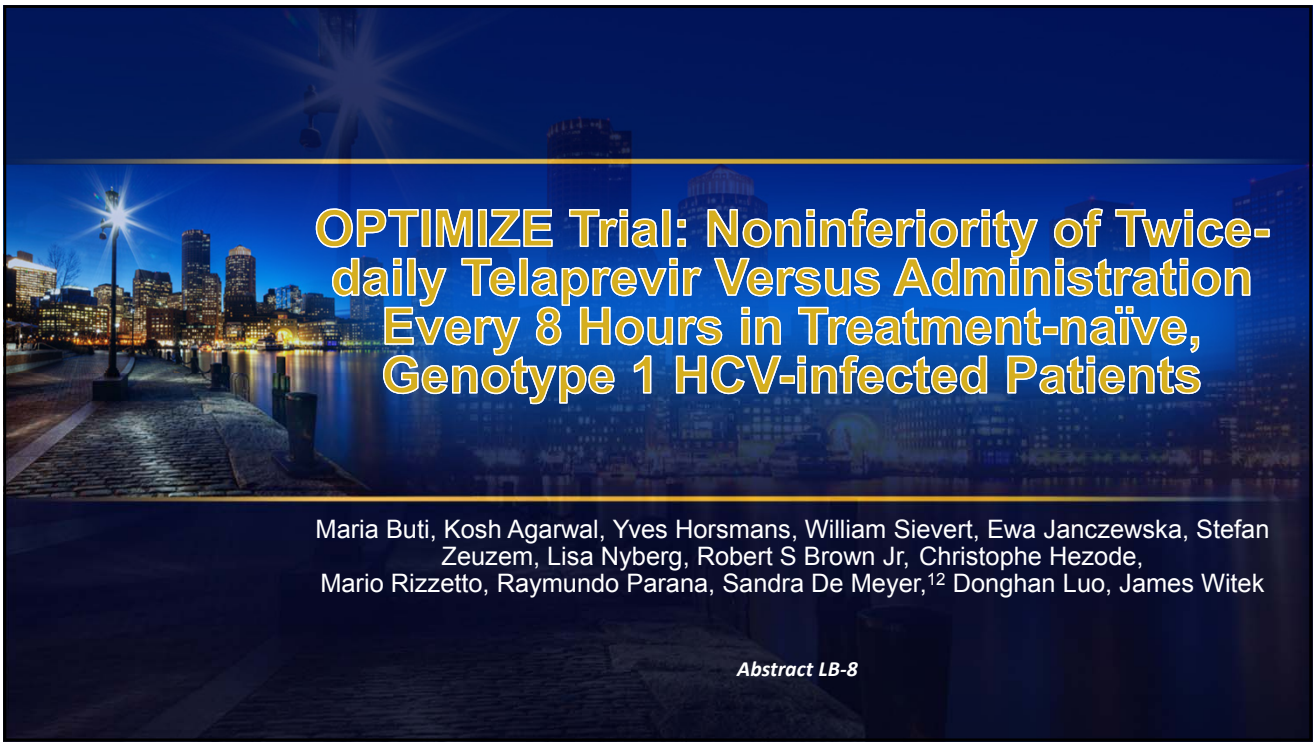
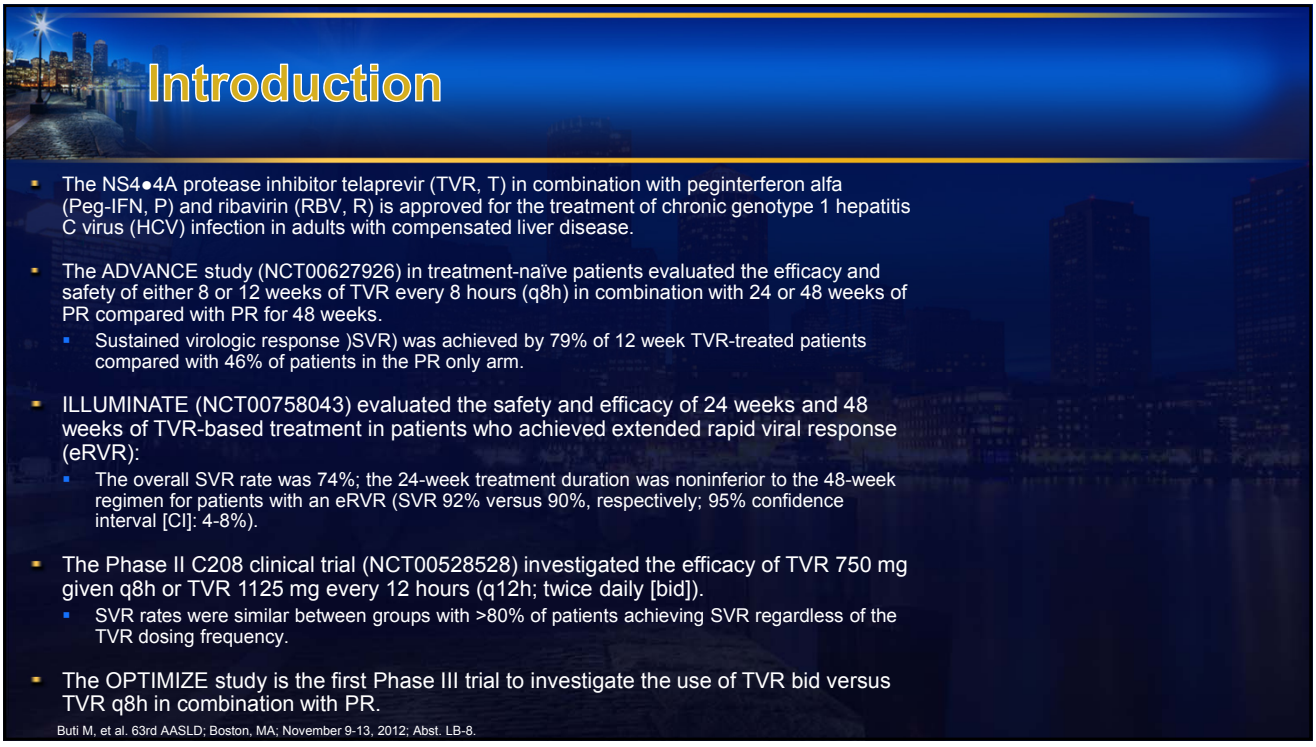


OPTIMIZE Trial: Noninferiority of Twice-daily Telaprevir Versus Administration Every 8 Hours in Treatment-naïve, Genotype 1 HCV-infected Patients

Maria Buti, Kosh Agarwal, Yves Horsmans, William Sievert, Ewa Janczewska, Stefan Zeuzem, Lisa Nyberg, Robert S Brown Jr, Christophe Hezode, Mario Rizzetto, Raymundo Parana, Sandra De Meyer,[12] Donghan Luo, James Witek

Abstract LB-8



Introduction

- The NS4●4A protease inhibitor telaprevir (TVR, T) in combination with peginterferon alfa (Peg-IFN, P) and ribavirin (RBV, R) is approved for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection in adults with compensated liver disease.
- The ADVANCE study (NCT00627926) in treatment-naïve patients evaluated the efficacy and safety of either 8 or 12 weeks of TVR every 8 hours (q8h) in combination with 24 or 48 weeks of PR compared with PR for 48 weeks.
  - Sustained virologic response)SVR) was achieved by 79% of 12 week TVR-treated patients compared with 46% of patients in the PR only arm.
- ILLUMINATE (NCT00758043) evaluated the safety and efficacy of 24 weeks and 48 weeks of TVR-based treatment in patients who achieved extended rapid viral response (eRVR):
  - The overall SVR rate was 74%; the 24-week treatment duration was noninferior to the 48-week regimen for patients with an eRVR (SVR 92% versus 90%, respectively; 95% confidence interval [CI]: 4-8%).
- The Phase II C208 clinical trial (NCT00528528) investigated the efficacy of TVR 750 mg given q8h or TVR 1125 mg every 12 hours (q12h; twice daily [bid]).
  - SVR rates were similar between groups with >80% of patients achieving SVR regardless of the TVR dosing frequency.
- The OPTIMIZE study is the first Phase III trial to investigate the use of TVR bid versus TVR q8h in combination with PR.

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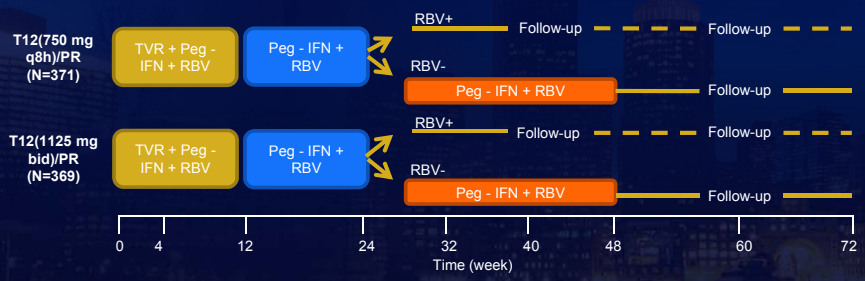
Optimize Study Design



- To minimize the risk of accumulation of mutations in patients without an adequate antiviral response and for consistency with standard guidelines for the treatment of genotype 1 chronic HCV infection, HCV RNA results were monitored to determine if treatment and procedural modifications should be made for individual patients
  - TVR was stopped if HCV RNA levels were >1000 IU/mL at Week 4 or ≥25 IU/mL at Weeks 12, 24, 32, or 40

RVR+ = patient achieved HCV RNA <25 IU/mL, target not detected at Week 4 of treatment.
All study drugs were stopped if HCV RNA levels were >1000 IU/mL at Week 4 or ≥25 IU/mL at Weeks 12, 24, 32, or 40.
Randomization was stratified by liver fibrosis status (F0-F2; F3-F4) and IL28B genotype (CC, CT, TT).
Peg-IFN alfa-2a 180 µg/week; RBV 1000-1200 mg/day; RVR = rapid virologic response.

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Study Objectives

- The primary objective of the OPTIMIZE trial was to demonstrate noninferiority in SVR12 (defined as plasma HCV RNA levels <25 IU/mL 12 weeks after the last planned dose of study drug) with TVR bid dosing compared with q8h dosing in combination with PR in treatment-naïve patients with genotype 1 chronic HCV infection.
- Secondary objectives were to evaluate:
  - The tolerability and safety of TVR when administered as 750 mg q8h or 1125 mg bid in combination with PR
  - The effect of *IL28B* genotype on viral response
  - The pharmacokinetics of TVR, Peg-IFN-alfa-2a and RBV, and pharmacokinetic-pharmacodynamic relationships for safety and efficacy
  - The changes from baseline in the amino acid sequence of the HCV NS3●4A region.

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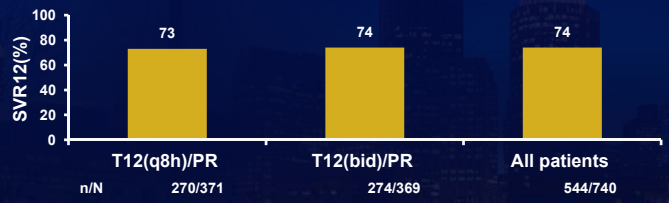
Efficacy



- Subgroup analyses for liver fibrosis stage and IL28B genotype showed similar SVR12 outcomes for T12 (bid)/PR and T12(q8h)/PR
  - In cirrhotic patients, SVR12 rates were 54% and 49% for T12 (bid)/PR and T12 (q8h)/PR, respectively
  - In non-cirrhotic patients, SVR12 rates were 78% and 77% for T12 (bid)/PR and T12 (q8h)/PR, respectively
- Subgroup analyses for a spectrum of baseline characteristics showed similar SVR12 outcomes for T12(bid)/PR and T12(q8h)/PR
- Total treatment duration was determined at Week 4 by RVR status. RVR was similar between T12(bid)/PR (69%)and T12(q8h)/PR (67%)
  - Overall, approximately two-third of patients were eligible tor the shortened treatment duration of 24 weeks of total therapy
  - SVR rates in RVR + patients were 86% and 85% for TI2(bid)/PR and T12(q8h)/PR, respectively
  - SVR rates in RVR- patients were 47% and 47% for TI2(bid)/PR and T12(q8h)/PR, respectively

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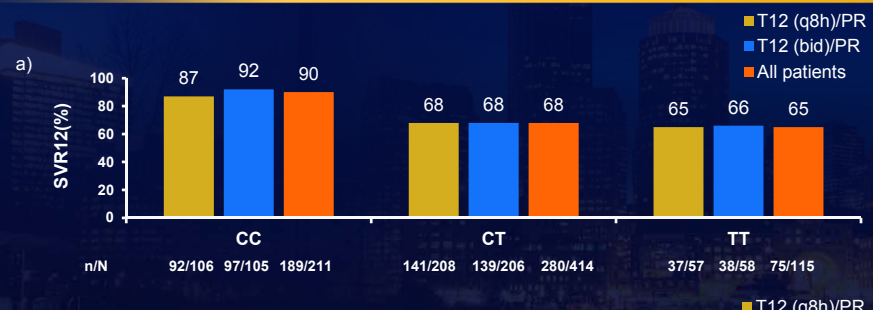
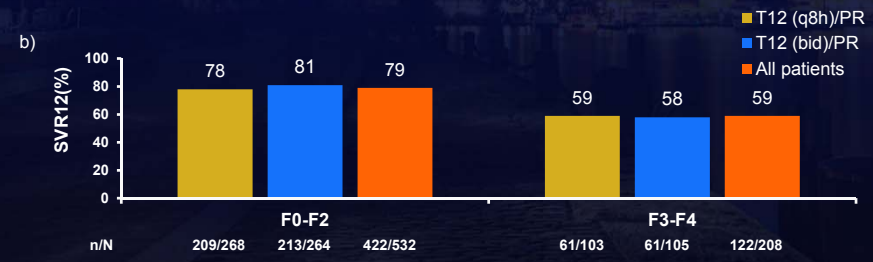
SVR12 in the T12(bid)/PR Group, T12(q8h)/PR Group and All Patients by a) *IL28B* Status and b) Liver Disease Status





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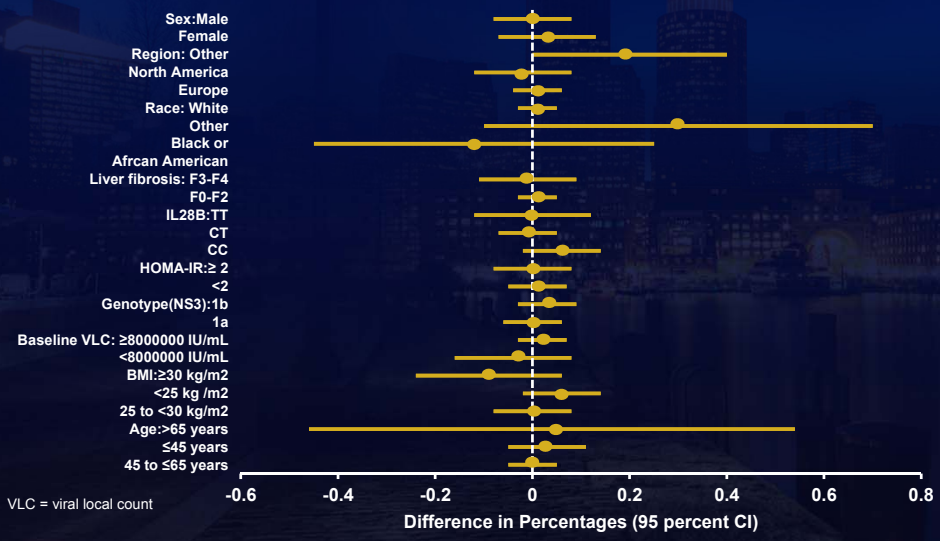
Study 103: Quad vs. TDF/FTC/ATV/r



VLC = viral local count

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Treatment Outcome

- Treatment outcome was similar between the T12(bid)/PR and T12(q8h)/PR arms with relapse seen in 8% vs 7% of patients, respectively

Treatment Outcome Classification.

Treatment outcome, n(%)	T12(q8h)/PR (N=371)	T12(bid)/PR (N=369)	All patients (N=740)
SVR12	270 (73)	274 (74)	544 (74)
Relapse*	19/293 (7)	23/300 (8)	42/593 (7)
On-treatment virologic failure*	36 (10)	38 (10)	74 (10)
Other	46 (12)	34 (9)	80 (11)

*Assessed in Patients with HCV RNA <25 IU/mL at the planned end of treatment.
Patients who met a virologic stopping rule or experienced viral breakthrough

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Adverse Events During the TVR Treatment Phase

Adverse event. N (%)	T12(q8h)/PR N=371)	T12(bid)/PR (N=369)	All Patients (N=740)
Any adverse event	367 (99)	360 (98)	727 (98)
Serious adverse event	35 (9)	28 (8)	63 (9)
Death*	1 (<1%)	0	1 (<1%)
Any Grade ≥3 adverse event	139 (38)	156 (42)	295 (40)
Grade ≥3 anemia SSC	70 (19)	95 (26)	165 (22)
Grade ≥3 rash SSC	22 (6)	18 (5)	40 (5)
Any Grade 4 adverse event	24 (7)	23 (6)	47 (6)
Any adverse event leading to permanent discontinuation of TVR	69 (19)	57 (15)	126 (17)
Any treatment related adverse event considered possibly related to TVR*	335 (90)	344 (93)	679 (92)
Most frequent adverse events*			
Fatigue	177 (48)	173 (47)	350 (47)
Pruritus SSC	(171 (46)	170 (46)	341 (46)
Anemia SSC	162 (44)	167 (45)	329 (45)
Nausea	142 (38)	128 (35)	270 (37)
Rash SSC	199 (54)	189 (51)	388 (52)
Headache	107 (29)	87 (24)	194 (26)

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Conclusions

- SVR12 rates for TVR 1125 mg bid were noninferior to TVR 750 mg q8h (74% versus 73%, respectively)
  - 28% of patients enrolled had advanced fibrosis (bridging and cirrhosis), 71% had non-CC *IL28B* genotype and 85% had HCV RNA ≥800000 IU/mL.
- SVR12 outcomes for T12(bid)/PR and T12(q8h)/PR were similar regardless of liver fibrosis status and *IL28B* genotype
- RVR and eRVR rates were similar in both arms
  - The majority (two-thirds) of patients were eligible to receive 24 weeks, total duration of therapy
- The safety and tolerability profile of T12(bid)/PR and T12(q8h)/PR was similar between treatment groups
- Similar SVR and adverse event rates achieved with 1125 mg bid TVR and 750 mg q8h TVR offers the potential of a simplified dosing regimen for genotype 1 HCV-infected patients

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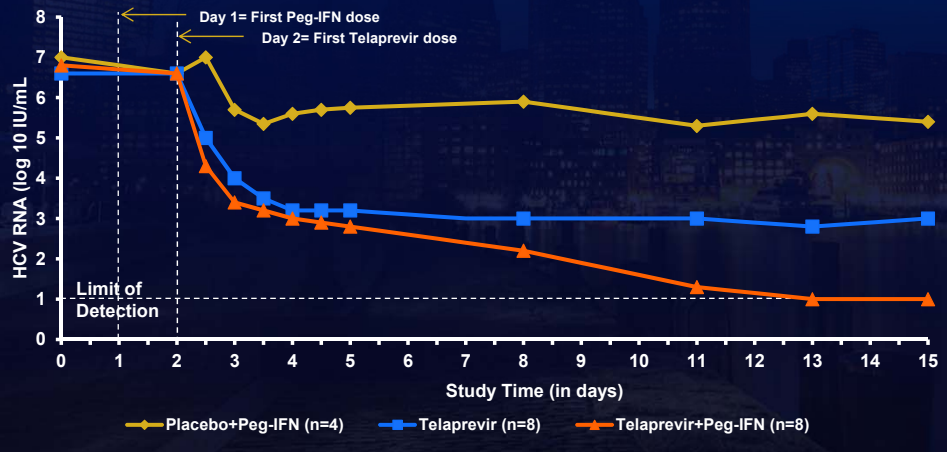
Preliminary Results of Twice Daily Dosing (Q12 hr) Of Telaprevir (TVR) for Treatment Naïve and Previously Treated Patients with Genotype 1 HCV: Comparable RVR, eRVR and SVR12 to Standard Daily Dosing at Q8 hr.

Paul Pockros, Douglas Hunt, Andrea Scherschel

Abstract 1830

Median HCV RNA Levels From Baseline to End Teleprevir (VX-950) Treatment

Plasma HCV RNA concentrations were determined using the Roche COBAS TaqMan HCV assay[3]



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Key Baseline Characteristics

Subgroup and Baseline Characteristics Treatment naive and previous relapse (TN)	no./total no. (%) n = 58
Genotype	
1a	33/58 (57%)
1b	13/58 (22)
Other	12/58 (21)
IL-28B genotype	
CC	9/37 (24)
Non-CC	28/37 (76)
F0-2 Fibrosis	32/58 (55)
F3-4 Fibrosis	26/58 (45)
Previous treatment failures (NR)	**n = 45**
Genotype	
1a	26/45 (58%)
1b	9/45 (20)
Other	10/45 (22)
IL-28B genotype	
CC	4/32 (12.5)
Non-CC	28/32 (87.5)
F0-2 Fibrosis	6/45 (13)
F3-4 Fibrosis	39/45 (87)

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Key Virologic Endpoints

Subgroup and End Point Treatment naive and previous relapse (TN)	no./total no. (%) n = 58
Undetectable at 4 wk	39/58 (67)
Undetectable or < 43 at 4 wk	55/58 (95)
Undetectable at 4 wk and 12 wk	37/58 (64)
Undetectable or < 43 wk at 4 wk + UND at 12 wk	51/58 (88)
SVR4	33/47 (70)
SVR 12	28/28 (100)
SVR24	14/14(100)
Relapse at 4 wk post-treatment	5/45 (11)
Previous treatment failures (NR)	n = 45
Undetectable at 4 wk	15/45 (33)
Undetectable or < 43 at 4 wk	34/45 (76)
Undetectable at 4 wk and 12 wk	15/45 (33)
Undetectable or < 43 wk at 4 wk + UND at 12 wk	30/45 (67)
SVR 4	15/35 (43)
SVR 12	12/12 (100)
SVR 24	7/7 (100)
Relapse at 4 wk post-treatment	2/35 (6)

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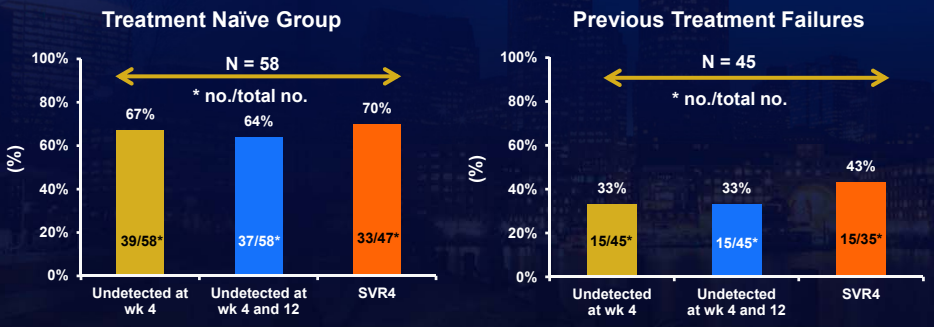
Naïve and Treatment Failures



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Early Discontinuation of Therapy

Subgroup and Baseline Characteristics Treatment naive and previous relapse (TN)	no./total no. (%) n = 58
Severe adverse effects	5/58 (8)
Decompensation	0/58 (0)
Viral breakthrough/failure to achieve milestone	4/58 (7)
Other	4/58 (7)
Total early discontinuation	13/58 (22)
Previous treatment failures (NR)	**n = 45**
Severe adverse effects	2/45(4)
Decompensation	4/45 (9)
Viral breakthrough/failure to achieve milestone	14/45 (31)
Other	3/45 (7)
Total early discontinuation	23/45 (51)
Previous treatment failures (NR)	**n = 103**
Severe adverse effects	7/103 (7)
Decompensation	4/103 (4)
Viral breakthrough/failure to achieve milestone	18/103 (17)
Other	7/103 (7)
Total early discontinuation	36/103 (35)

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Adverse Events and Lab Abnormalities

SEVERE ADVERSE EVENTS REQUIRING DISCONTINUATION OF THERAPY

Type of Adverse Even n = 103 total study patients	No./total no. (%)
Anemia	2/103 (2)
Nausea, vomiting	2/103 (2)
Constitutional symptoms	1/103 (1)
DRESS syndrome	1/103 (1)
Thrombocytopenia	1/103 (1)
Total severe adverse events	7/103 (7)

MANAGEMENT OF LABORATORY ABNORMALITIES CAUSED BY THERAPY

Type of Adverse Event n = 103 total study patients	No./total no. (%)
RBV dose reductions for Hgb<10g	49/103 (47.5)
EPO use for anemic patients	45/103 (44)
Platelet growth factor use	6/103 (6)
Neutriphil growth factor	2/103 (2)
Total patients with growth factor use	46/103
Transfusions	14/103 (18.5)

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