Sustained Virologic Response (SVR) in Prior PegInterferon/Ribavirin (PR) Treatment Failures After Retreatment with Boceprevir (BOC) + PR: PROVIDE Study Interim Results

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Background

- Addition of boceprevir (BOC) to peginterferon + ribavirin (PR) for treatment of chronic HCV genotype 1 infection leads to significantly higher rates of sustained virologic response (SVR) in
  - previously untreated patients (SPRINT-2)[1]
  - previously treated patients (RESPOND-2)[2]
- RESPOND-2 included patients with either a partial response or a relapse response to a prior course of PR
  - Patients with a null response were excluded
- SVR rate in null responders retreated with PR is typically below 15%
- Ongoing challenge to achieve SVR for patients with CHC who have not responded to prior PR therapy

1. Poordad et al. New Engl J Med 2011;364(13):1195; 2. Bacon et al. N Engl J Med 2011;364(13):1207.

Goal

- To define the SVR rate of well-documented null responders to prior P/R therapy when retreated with boceprevir in combination with peginterferon and ribavirin.

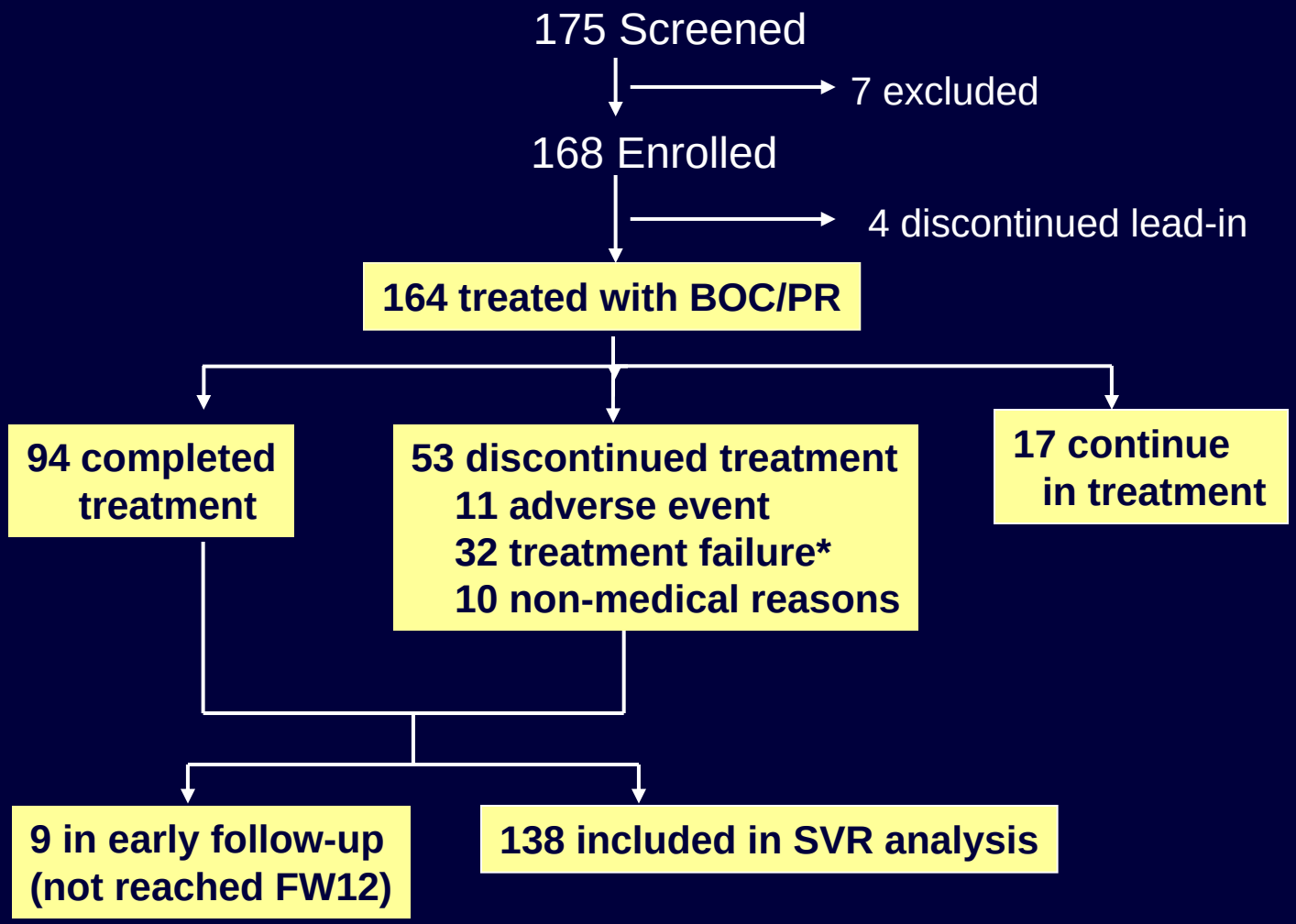
Methods

- Study Design: Open-label, single-arm, multicenter rollover study
- Patient Population:
  - Subjects from control arm of Phase 2/3 BOC studies who received ≥12 weeks of PR treatment AND failed to achieve SVR due to:
    - Futility, defined as detectable HCV RNA (Roche TaqMan, LLD = 9.3 IU/mL) at TW12 (treatment-experienced patients) or TW24 (previously untreated patients)
    - Virologic breakthrough
    - Relapse after end of treatment (EOT) response
  - Patients were enrolled in PROVIDE at the discretion of the site investigators
- PROVIDE study enabled observation of historic Null responders

Methods (II)

- Patients received 4-week PR lead-in if enrolled >2 weeks since completing the previous study
- Following lead-in, triple therapy administered for up to 44 weeks:
  - Boceprevir 800 mg orally TID
  - PEG2b 1.5 µg/kg s.c. once weekly
  - Ribavirin 600-1400 mg/day (by weight) orally in 2 divided doses
- Futility stopping rule: Detectable HCV RNA at TW12
- Primary endpoint of SVR
  - undetectable HCV RNA 24 weeks post therapy
  - FW12 HCV-RNA result carried forward if no FW24 value
  - Prespecified analysis limited to patients who received at least one dose of BOC

Study Flow (Interim Analysis)

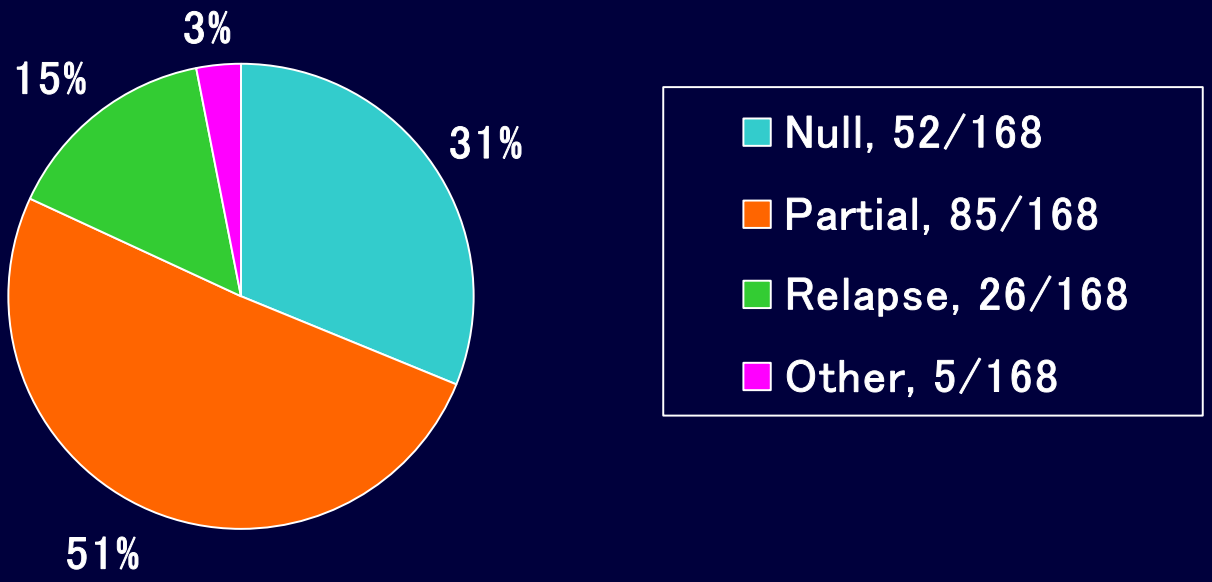


* Includes subjects who discontinued due to futility at TW12 or had virologic breakthrough or incomplete virologic response.

Response to PR Treatment in Prior Study†

Null response	<2 log decrease in HCV RNA at TW12 of PEG/RBV
Partial response	≥2 log decrease in HCV RNA by TW12 and detectable HCV RNA at end of treatment
Relapse	undetectable HCV RNA at end of prior treatment and detectable HCV RNA at end of follow-up
Other	not in the above categories of prior treatment failure

† Prior Study: SPRINT-1, n=2; SPRINT-2, n=81; RESPOND-2, n=45; BOC/Pegasys, n=36.



Patient Disposition by Prior Treatment Response

	Prior Null Response (N = 52)	Prior Partial Response (N = 85)	Prior Relapse (N = 26)
Treated with BOC/PR	49	85	25
Ongoing treatment	2 (4)	4 (5)	10 (40)
Completed 44 wks BOC/PR	21 (43)	60 (71)	9 (36)
Discontinued treatment	26 (53)	21 (25)	6 (24)
Adverse event	2 (4)	6 (7)	3 (12)
Treatment failure	22 (45)	10 (12)	0
BT or IVR	15 (29)	8 (9)	0
TW12 futility	7 (13)	2 (2)	0
Non-medical reason	2 (4)	5 (6)	3 (12)
Completed or discontinued	47 (96)	81 (95)	15 (60)
In early follow-up (< FW12)	0	3 (4)	6 (24)
Included in SVR analysis	47 (96)	78 (92)	9 (36)

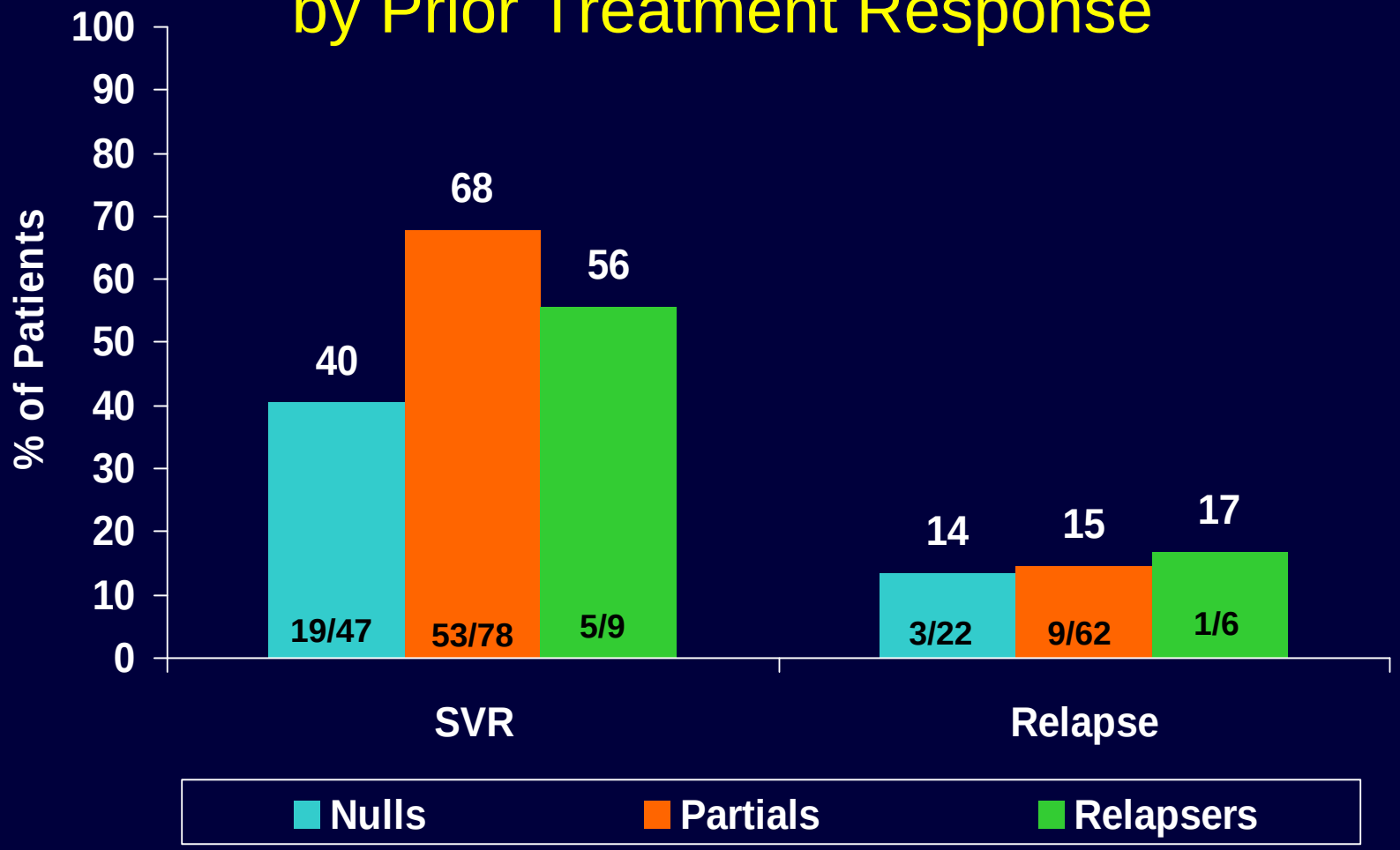
Data shown as n (%) of patients, using the number treated with BOC/PR as denominator for calculation of %.
Table does not include 5 patients whose prior non-response could not be classified as null, partial, or relapse; one is ongoing in treatment, and 4 have completed treatment and are included in SVR analysis.
BT, viral breakthrough; IVR, incomplete virologic response.

Baseline Patient Characteristics

	Prior Null Response (N = 52)	Prior Partial Response (N = 85)	Prior Relapse (N = 26)
Male, n (%)	33 (63)	60 (71)	17 (65)
White, n (%)	36 (69)	74 (87)	26 (100)
Age (y), mean ± SD	51.3 ± 7.7	52.6 ±8.4	53.9 ± 6.6
BMI† (kg/m^2), mean ± SD	26.8 ± 3.8	28.7 ±4.7	27.4 ± 4.3
VL >800,000 IU/mL, n (%)	46 (88)	68 (80)	16 (62)
HCV subtype§, n (%): 1a	34 (65)	47 (55)	18 (69)
1b	18 (35)	36 (42)	8 (31)
Metavir Score§, n (%): F0-2	46 (88)	63 (74)	22 (85)
F3-4	5 (10)	19 (22)	2 (8)
missing	1 (2)	3 (4)	2 (8)

Does not include 5 patients whose prior non-response could not be classified as null, partial, or relapse.
† using height from parent study, weight at entry in PROVIDE.
§ measured at entry in parent study; HCV subtype missing for 2 patients with prior partial response.

SVR and Relapse† Rates, by Prior Treatment Response

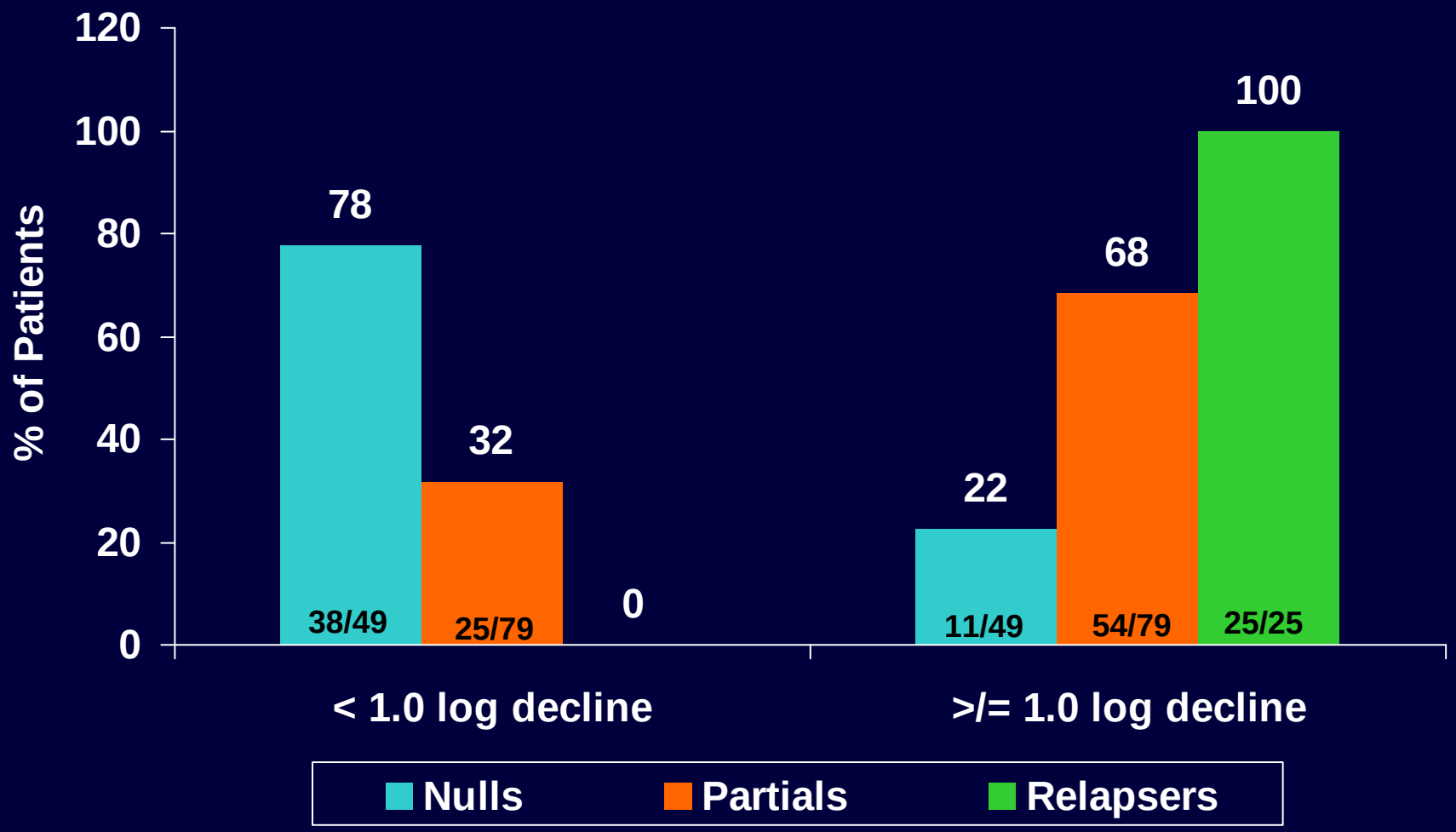


- SVR was also achieved in all 4 patients with 'other' prior non-response.
- Overall, 81 of 138 patients (59%) achieved SVR.

SVR rates if lead-in dropouts included: nulls 38% (19/50), partials 68% (53/78), relapsers 50% (5/10), overall 57% (81/142).

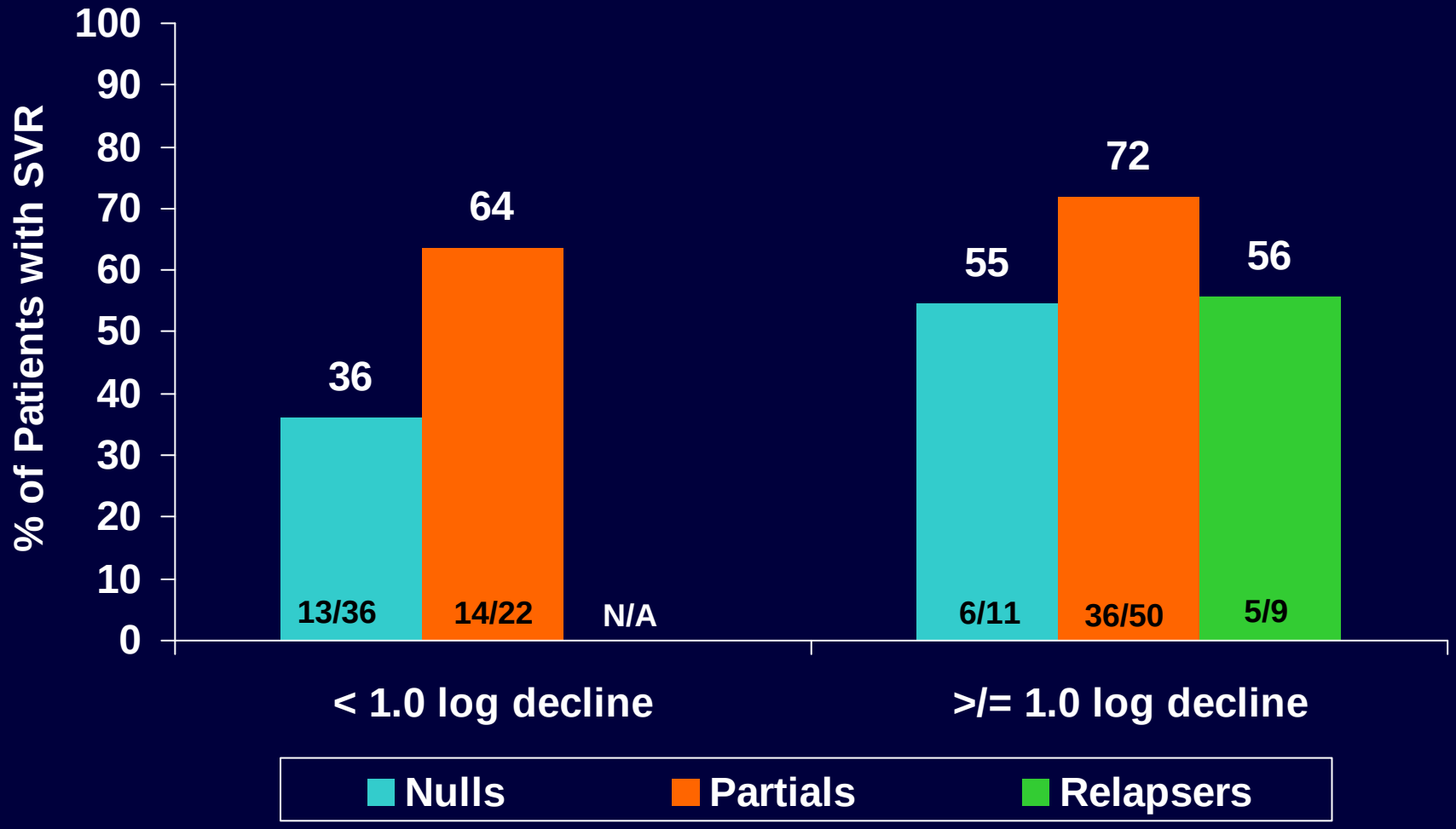
† denominator for relapse rate = patients with undetectable HCV RNA at EOT and not missing end of follow-up data.

Relationship of Week 4 Lead-In Response† to Prior Treatment Response



† Excludes 4 subjects who dropped out during lead-in, and 8 subjects who were direct enrollers (no PR lead-in).

Relationship of SVR by Week 4 Lead-In Response† and Prior Treatment Response



† Excludes 4 subjects who dropped out during lead-in and 8 subjects who were direct enrollers (no PR lead-in).

SVR by Baseline Characteristics and Prior Treatment Response

	SVR, n/m (%)		
	Prior Null Response	**Prior Partial Response**	**Prior Relapse**
Male	14/30 (47)	42/55 (76)	4/7 (57)
Female	5/17 (29)	11/23 (48)	1/2 (50)
Black	3/12 (25)	3/6 (50)	NA
Non-Black	16/35 (46)	50/72 (69)	5/9 (56)
Age <50	11/20 (55)	21/25 (84)	0/1 (0)
Age ≥ 50	8/27 (30)	32/53 (60)	5/8 (63)
BMI ≤ 25	5/16 (31)	9/17 (53)	2/3 (67)
BMI > 25	14/31 (45)	44/60 (73)	3/5 (60)

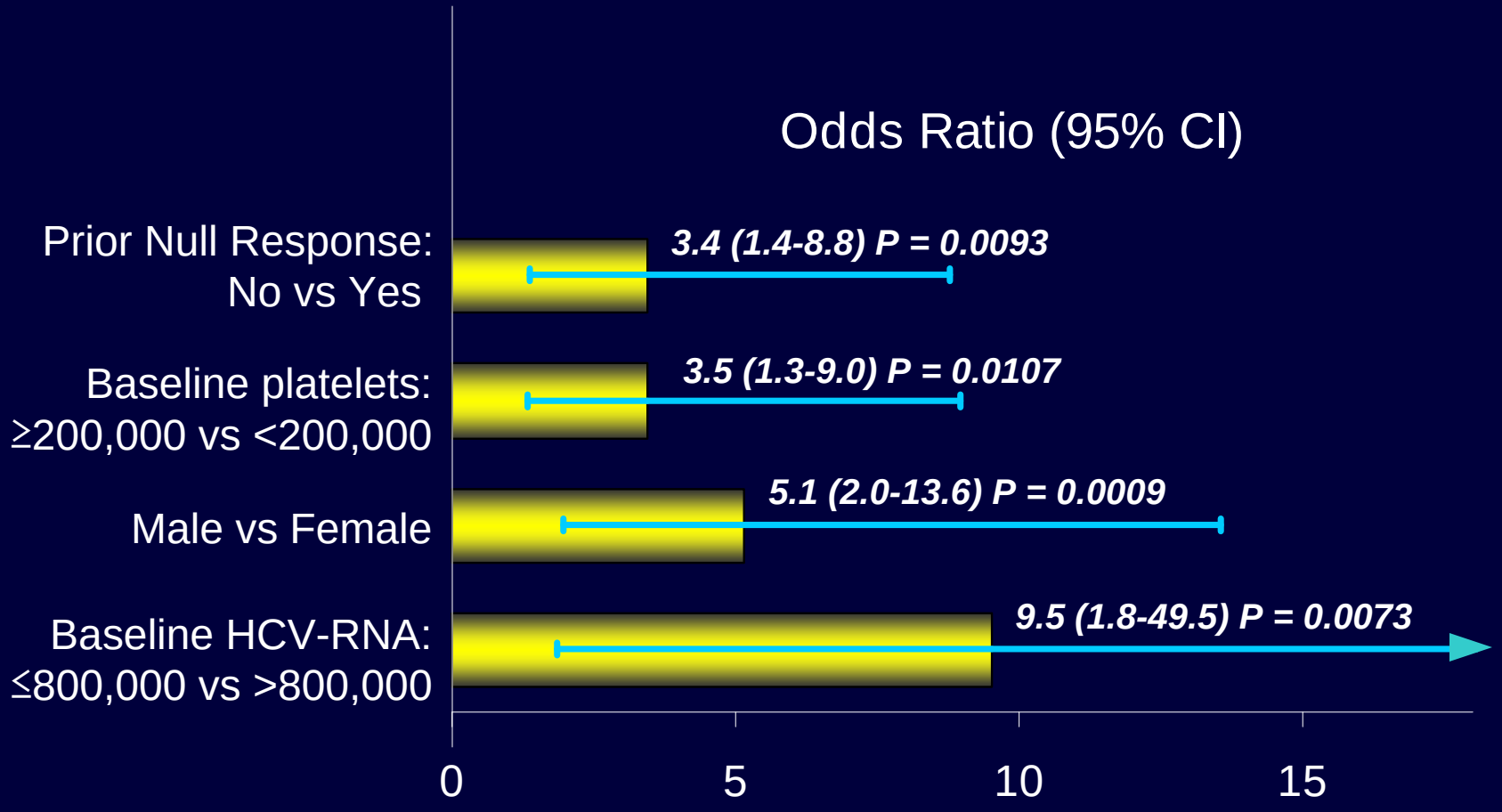
NA, not applicable as there were no black patients in the prior relapse group.

SVR by Baseline Characteristics and Prior Treatment Response (con't)

	SVR, n/m (%)		
	Prior Null Response	**Prior Partial Response**	**Prior Relapse**
VL ≤800,000	4/6 (67)	13/17 (76)	2/3 (67)
VL >800,000	15/41 (37)	40/61 (66)	3/6 (50)
F0/1/2	17/41 (41)	37/56 (66)	3/6 (50)
F3/4	2/5 (40)	15/19 (79)	1/1 (100)
HCV G1a‡	14/31 (45)	31/43 (72)	4/8 (50)
HCV G1b‡	5/16 (31)	21/34 (62)	1/1 (100)
Platelets <200,000	2/12 (17)	19/35 (54)	1/3 (33)
Platelets ≥200,000	17/34 (50)	34/43 (79)	4/6 (67)

‡ HCV subtype in referring study as determined by Janssen (Virco) assay based on sequencing of domain p329bp in the NS5B polymerase gene.

Baseline Factors as Predictors of SVR (Multiple Stepwise Logistic Regression Model)



The figure shows only covariates that were significant ($p<0.05$) and retained in the model after using a step-wise procedure. Factors entered but not retained in the model were age, HCV genotype, race, weight, BMI, fibrosis, steatosis, and ALT.

Summary of Adverse Events

	All Treated Patients N=168
Treatment-emergent AE	161 (96)
Serious AE	17 (10)
Death	0
Life-threatening AE	0
Study drug discontinued† due to AE	12 (7)
Dose modification† due to AE	53 (32)

Data shown as number (%) of patients.

† Patients with dose modification and study drug discontinued due to AE were counted only in the category for study drug discontinued due to AE.

Most Common† Adverse Events

	All Treated Patients N=168
Anemia	80 (48)
Neutropenia	37 (22)
Diarrhea	37 (22)
Dysgeusia	57 (34)
Nausea	50 (30)
Fatigue	79 (47)
Flu-like illness	35 (21)
Headache	45 (27)
Insomnia	38 (23)

Data shown as number (%) of patients.

† Incidence > 20%.

Anemia-related Events

	All Treated Patients N=168
Hemoglobin < 10 g/dL	84 (50)
8.5 to < 10	66 (39)
< 8.5	18 (11)
WHO Grade 1 (9.5 to <11.0)	60 (36)
Grade 2 (8.0 to <9.5)	49 (29)
Grade 3 (6.5 to <8.0)	5 (3)
Grade 4 (<6.5)	0
Study drug discontinued due to AE	1 (1)
Dose modification† due to AE	44 (26)
Erythropoietin use	68 (40)
RBC Transfusion	4 (2)

Data shown as number (%) of patients.

† Excludes subjects who discontinued study drug due to AE.

Conclusions

- In prior null responders to PR therapy, treatment with BOC/PR in the PROVIDE study achieved an SVR rate of 40%.
- Thus, BOC/PR therapy is efficacious in patients with all 3 types of non-response: relapsers, partial responders and null responders.
- The safety profile of BOC/PR in the PROVIDE study was comparable to that previously reported for BOC/PR

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Back-up Data (lead-in response)

PR Lead-in Response by Prior Treatment Response (41% of patients had <1 log decline at TW4)

	BOC/PR Treated Patients, % (n/N)			
Lead-in Response (Viral Load Reduction from BL)	Prior Null Responders n=49	Prior Partial Responders n=79	Prior Relapsers n=25	Prior Other Nonresponders n=3
<1.0 log_{10} Decline	**77.6 (38/49)**	**31.6 (25/79)**	**N/A**	**33.3 (1/3)**
<0.5 log	34.7 (17/49)	6.3 (5/79)	N/A	33.3 (1/3)
0.5-<1 log	42.9 (21/49)	25.3 (20/79)	N/A	N/A
≥1.0 log_{10} Decline	**22.4 (11/49)**	**68.4 (54/79)**	**100.0 (25/25)**	**66.7 (2/3)**

Note: Includes ongoing patients; excludes 4 patients who dropped out during lead-in and 8 patients who were direct enrollers without 4-week PR lead-in in this study.

Relationship Between SVR Rates and HCV RNA Decline After 4 Week PR Lead-in

	SVR % (n/N)[a]			
	BOC/PR Treated Subjects			
Lead-in Response (Viral Load Reduction from Baseline)[b]	Prior Null Responders n=47	Prior Partial Responder n=72	Prior Relapsers n=9	Other Prior Non-Responders n=2
<1.0 log_{10} Decline	**36.1 (13/36)**	**63.6 (14/22)**	**N/A**	**100.0 (1/1)**
<0.5	35.3 (6/17)	75.0 (3/4)	N/A	100.0 (1/1)
0.5-<1	36.8 (7/19)	61.1 (11/18)	N/A	N/A
≥1.0 log_{10} decline or Negative	**54.5 (6/11)**	**72.0 (36/50)**	**55.6 (5/9)**	**100.0 (1/1)**

Includes patients (N) who received boceprevir and had lead-in and SVR assessments available at the time of the interim analysis. Patients who discontinued early were considered missing (treatment failures). If a patient was missing FW 24 data, the FW 12 value was carried forward to FW 24 for SVR. Excludes 4 patients who dropped out during lead-in and 8 patients who were direct enrollers without 4−week PR lead-in. Also excludes patients who are still on treatment or in early follow-up.