



Direct-Acting Antivirals: A New Era for the Treatment of Chronic Hepatitis C

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Antiviral Drugs Advisory Committee
Meeting

April 27- 28, 2011

Silver Spring, MD

Background

- Chronic Hepatitis C (CHC) is a global problem
 - ~ 180 million infected worldwide
- CHC is a domestic problem
 - ~ 3-4 million of the US population are chronically infected
 - Of the 5.6 million Veterans in VHA care in 2008, 2.6% had a diagnosis of CHC
 - Incidence of infection in US is decreasing but CHC related complications are increasing: cirrhosis, HCC
 - With aging of infected population, more liver related complications are expected in the next 10 – 20 years
- CHC already the most common reason for liver transplant²

Populations described in FDA Draft HCV Guidance

Naïve: received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

Null Responder: less than 2 log₁₀ reduction in HCV RNA at week 12 of a Peg Interferon/RBV regimen

Partial Responder: greater than or equal to 2 log₁₀ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a Peg-Interferon/RBV regimen

Responder Relapser: HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up

Early Response Definitions

- Rapid Virologic Response (RVR)
 - Undetectable HCV RNA at week 4
- Extended RVR (eRVR)
 - Undetectable HCV RNA at weeks 4 and 12

Sustained Virologic Response (SVR24)

- Validated endpoint
- Defined as absence of detectable RNA in serum 6 months after completion of therapy
- Best indicator of successful therapy of CHC
- Achieving SVR
 - Fewer liver-related complications
 - Less progression to HCC
 - Fewer liver-related deaths and possibly improvement in all-cause mortality

Pearlman and Traub, CID, 2011

Standard of Care (SOC)

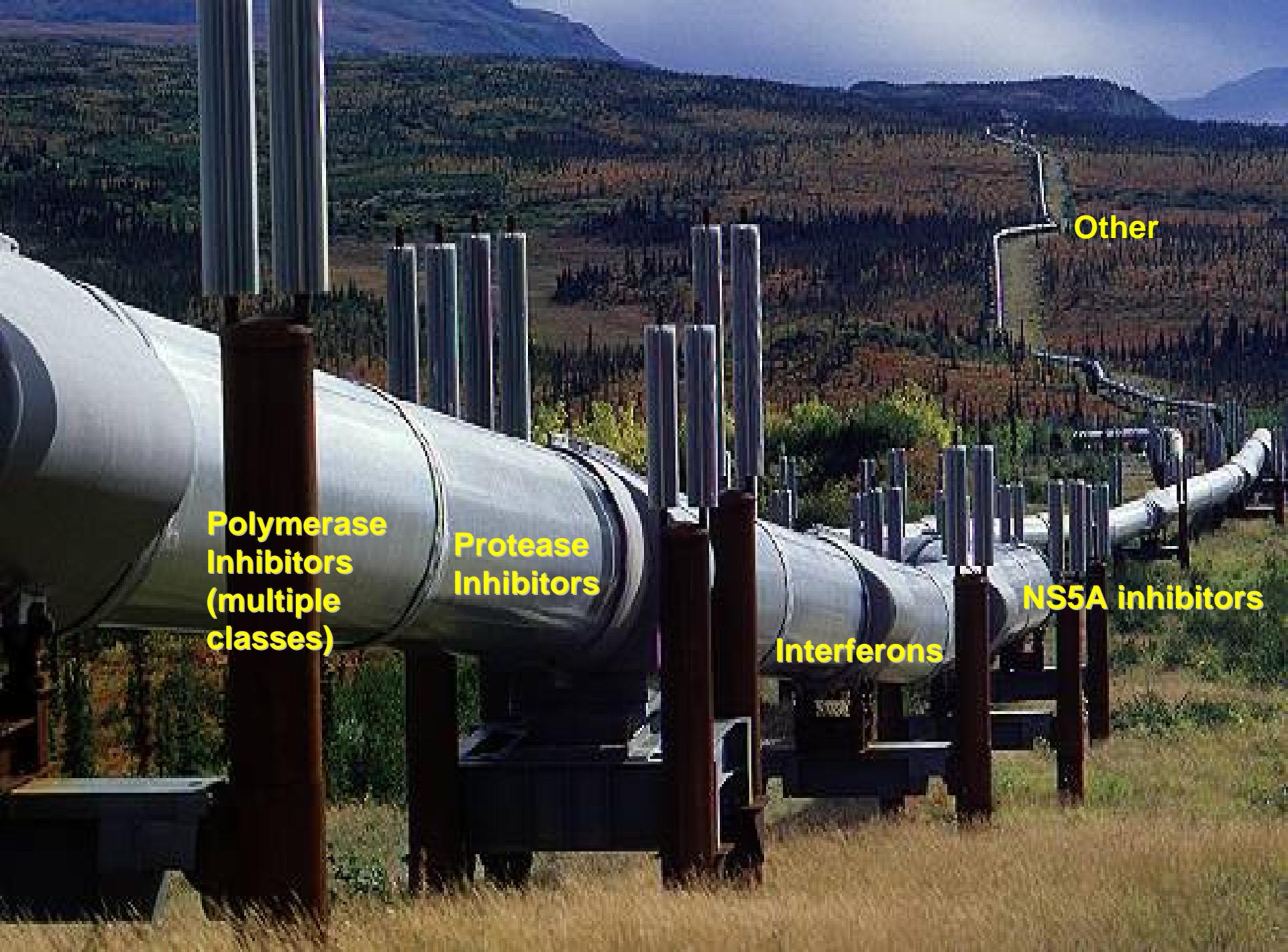
- Currently, the SOC for treatment of CHC is pegylated interferon with ribavirin
- Treatment duration is 48 weeks for Genotype 1 and 24 weeks for Genotypes 2 and 3
- Response rates average 50% (20%-80%)
 - Depend on multiple factors
 - Genotype, IL28B status, race, viral load, etc.
- Significant toxicities seen with SOC

Response Guided Therapy (RGT)

- Treatment algorithm individualizing treatment based on virologic response
- Goals of RGT
 - 1. shorten therapy if possible in those who exhibit favorable viral kinetics
 - 2. identify subjects who are unlikely to have a response
 - Limit side effects
 - Cost

FDA Pharmacometric Analyses

- New concept to determine duration of therapy in different populations
- Treatment naïve population already contains subpopulations of each possible PR responder group
 - Data for how treatment experienced patients may respond are within data from treatment naïve patients
 - Prior non-responders demonstrate similar virologic response at week 4 of initial or subsequent PR treatment
- Early virologic response may be more important than previous exposure to PR



**Polymerase
Inhibitors
(multiple
classes)**

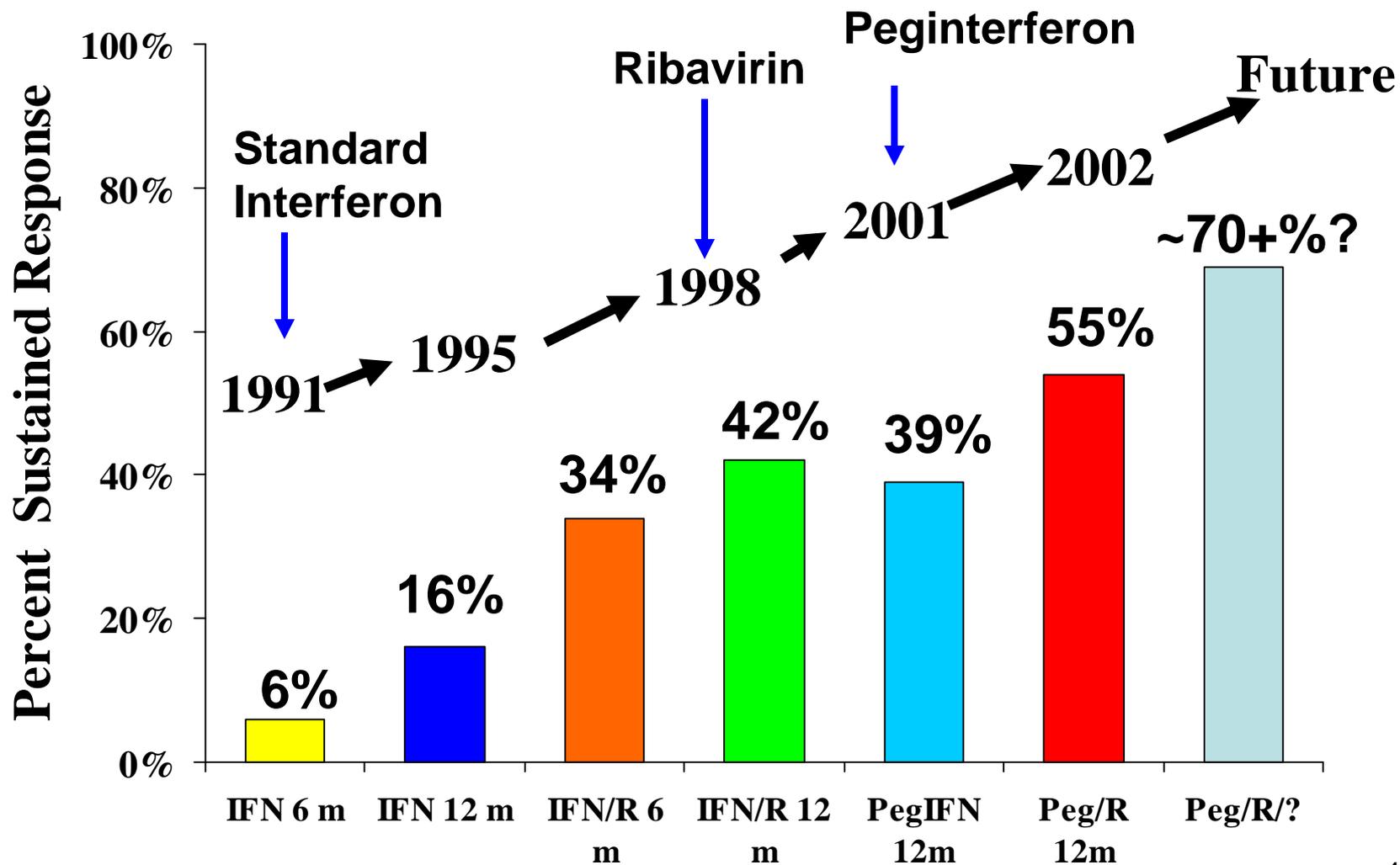
**Protease
Inhibitors**

Interferons

NS5A inhibitors

Other

Milestones in Therapy of CHC





Antiviral Drugs Advisory Committee
April 27, 2011
Victrelis (boceprevir),
Merck & Co., Inc.

Jeff Murray, MD, MPH
Deputy Director
Division of Antiviral Products

Outline

- Today's Agenda
- The Committee
- Balancing Risks and Benefits
 - Clinical Benefit of SVR
 - Treatment Availability vs. Complete Information
 - Treatment Duration and Benefit/Risk
- Considering Postmarketing Trials/Studies

Today's Agenda

- Opening Remarks
- Presentation: Merck
- Presentation: FDA
- Lunch
- Open Public Hearing
- Questions from the Committee
- Questions To the Committee

Questions to the Committee

a short-hand version

1. Comment on Safety
2. Overall Risk-Benefit AND Vote
3. Include Null Responders?
4. Response Guided Therapy-best duration
 - a. Treatment Naive Late Responders
 - b. Black Patients
 - c. Patients with Fibrosis/Cirrhosis
5. Postmarketing Studies/Trials

Antiviral Drugs Advisory Committee

- Members/Consultants
 - Hepatologists,
 - Infectious Disease Specialists, HIV Specialists
- Lessons learned from HIV may be helpful. Caution: Not to over generalize
- Example: Treatment “Naive”
 - HIV Antiretrovirals: Implies WT virus, Majority Expected to Respond. Homogeneity.
 - HCV Interferon: Majority expected NOT to have complete response to Peg-IFN/RBV. Heterogeneity.
 - Concept: Naive patients contain patients who will be responders, relapsers, partial responders and null responders

Risk vs. Benefit

Adding a Direct
Acting Antiviral to
PEG-IFN/RBV



Sustained Virologic Response (SVR)

Pearlman and Traub, CID 2011

- Clinically “Validated” Endpoint
- Multiple (19) cohort studies comparing outcomes between SVR and NR showing:
 - ↓ decompensated liver disease,
 - ↓ hepatocellular carcinoma,
 - ↓ diabetes
 - ↓ liver mortality
 - ↓ overall mortality

Veteran's Affairs Cohort

Backus, Hepatology 2010

- 16,864 HCV infected patients, high rates of co-morbidities (smoking, diabetes, etc.)
- All treated with Peg-IFN/RBV
- 7,420 patients had SVR
- Reduction in Overall Mortality:

Risk (SVR vs. NR) = 0.67 (.56-.79)
for Genotype 1

Information vs. Availability

***Treatment
Availability for a
Serious Illness***

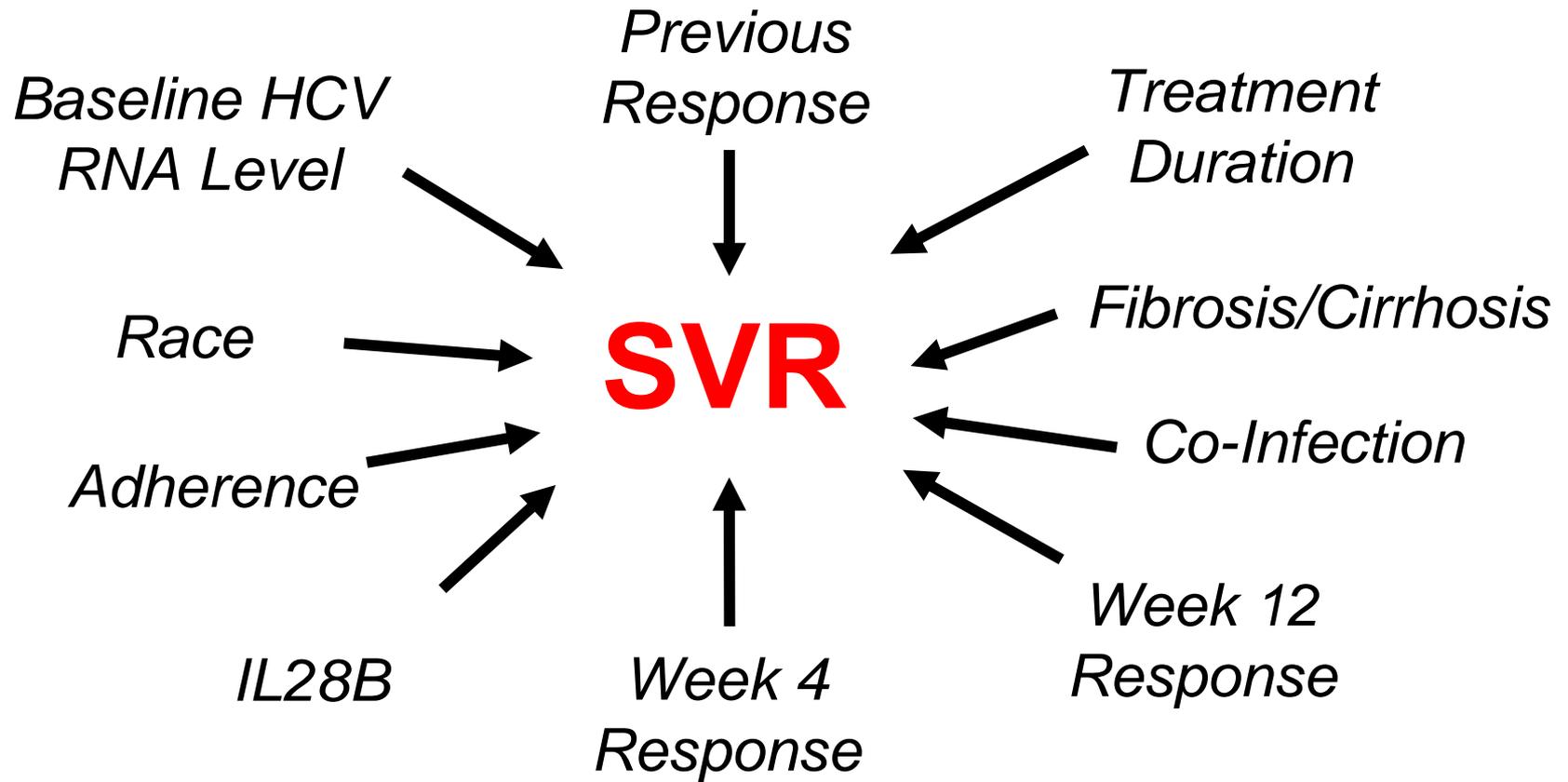


***Complete
Information***



A Good Phase 3 Trial Answers Questions AND Generates New Questions

Interplay of Many Factors



Risk vs. Benefit

Duration of Treatment for Subgroups

↑ **SVR**



↓ **Toxicity**

Need Labeling Recommendations Despite Uncertainty or Incomplete Data

Postmarketing Studies/Trials

- Trials: Prospective Clinical; Studies: Nonclinical, Clinical Cohort
- Requirements
 - Pediatric Trials (PREA)
 - Accelerated Approval: Confirm Clinical Benefit
 - Safety Issues (FDAAA of 2007)

Postmarketing Studies/Trials

- Safety Issues (FDAAA of 2007)
 - Adverse Reactions: signal confirmation and evaluation, frequency, severity, risk factors, management,
 - Drug-Drug Interactions
 - Drug Resistance
- Commitments
 - New indications/efficacy, exploratory studies based on theoretical hypotheses, long term follow-up without specific safety concerns



Boceprevir NDA 202258 FDA Analyses

Poonam Mishra, M.D.
Jeffry Florian, Ph.D.

on behalf of
Boceprevir Review Team
Division of Antiviral Products

Antiviral Drugs Advisory Committee Meeting
April 27, 2011

Presentation Outline

- Clinical Safety
 - Safety concern related to Anemia and overall Bone Marrow Suppressive Effects
- Clinical Virology
- Efficacy Discussions
 - Trial Designs and Key Terminology
 - Primary Efficacy Results and Pertinent Subgroup Analysis
 - Issue of proposed indication in Null-Responders
 - Optimal Duration of therapy in patient populations of concern

Safety Issues

Focus: Hematologic Adverse Events

- **Anemia**
- **Neutropenia**
- **Thrombocytopenia**

Hematologic Adverse Events Phase 3 Trials Analyzed

- P05216 (SPRINT-2)- In previously untreated subjects (treatment-naïve)
- P05101 (RESPOND-2)- In previous treatment-failure subjects (treatment-experienced)

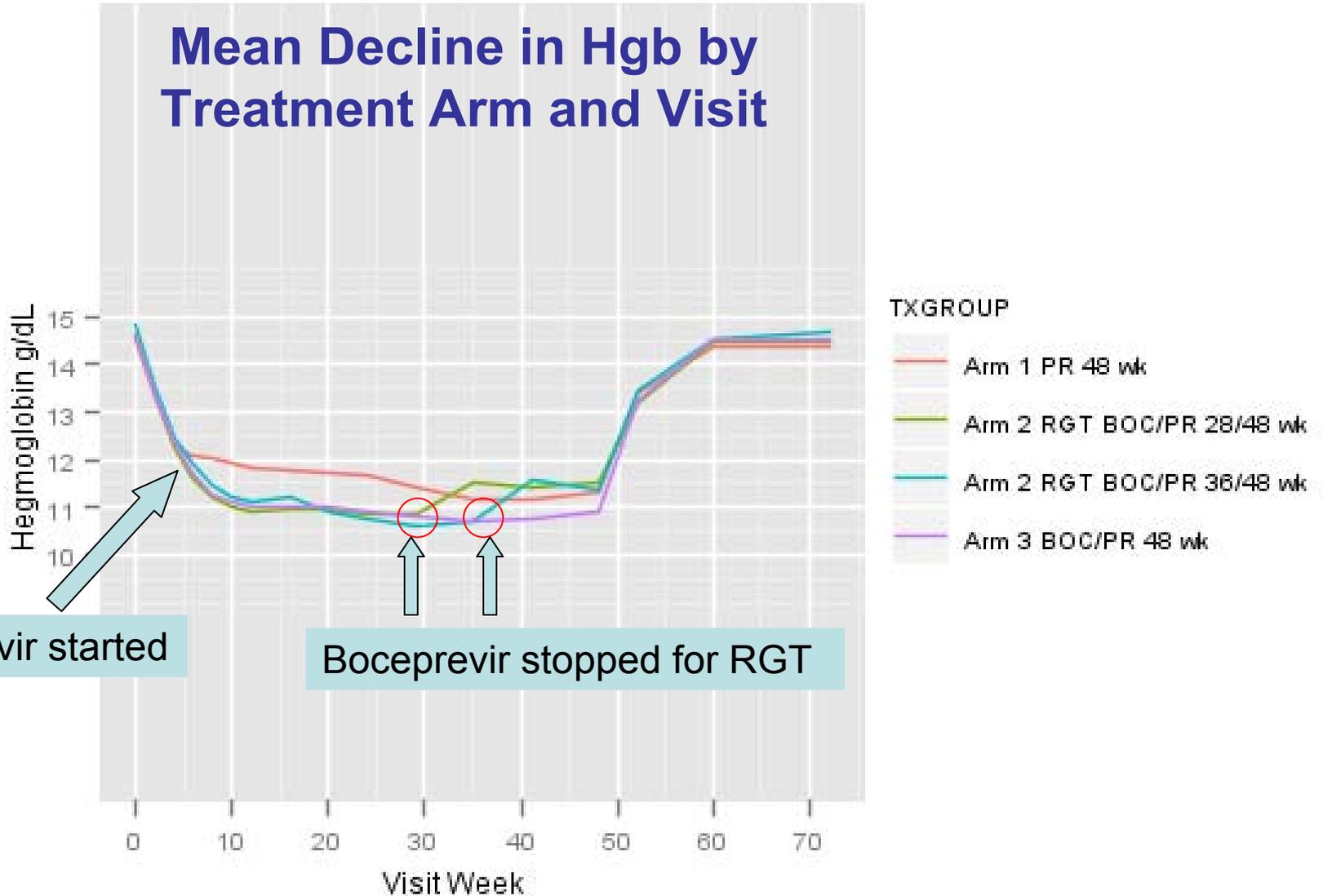
Anemia in Phase 3 Trials

	BOC/PR N = 1057 n (%)	PR N=443 n (%)
Anemia (Clinical Adverse Event)	548 (52)	131 (30)
Anemia (Laboratory Event) Hgb ≤ 10 g/dL Hgb ≤ 8.5 g/dL	547 (52) 92 (9)	141 (32) 16 (4)
Serious Anemia Adverse Event	12 (1)	1 (<1)
Anemia resulting in: Drug Discontinuation (any drug) Dose Reduction (any drug) Dose Interruption (any drug)	19 (2) 264 (25) 31 (3)	4 (1) 58 (13) 9 (2)

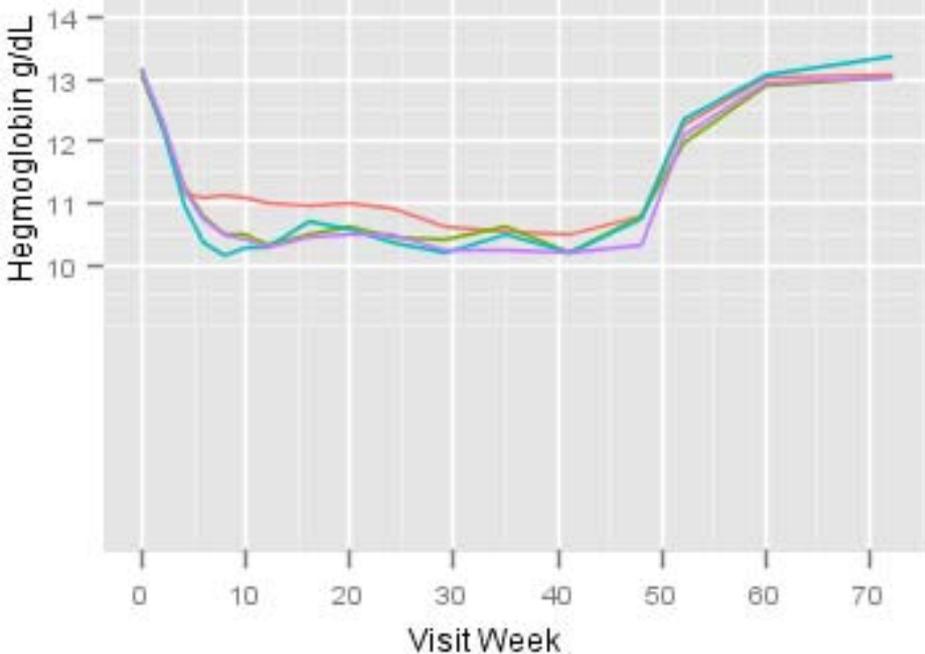
Challenges in the Assessment of Anemia

- Assessment of anemia was confounded by baseline hemoglobin (Hgb).
- Subjects with lower baseline Hgb had higher rates of:
 - Nadir Hgb ≤ 10 g/dL
 - Anemia adverse events reported
 - Interventions for anemia management
 - BUT also had smaller magnitude of Hgb decline
- Boceprevir-treated subjects experienced additional decline in Hgb:
 - Mean Hgb decline beyond that with PR was $\sim +1$ g/dL
 - In some subjects additional Hgb decline was greater than 1g/dL
- However, assessment of risk by absolute maximum Hgb decline is difficult to interpret because of differential post-baseline interventions

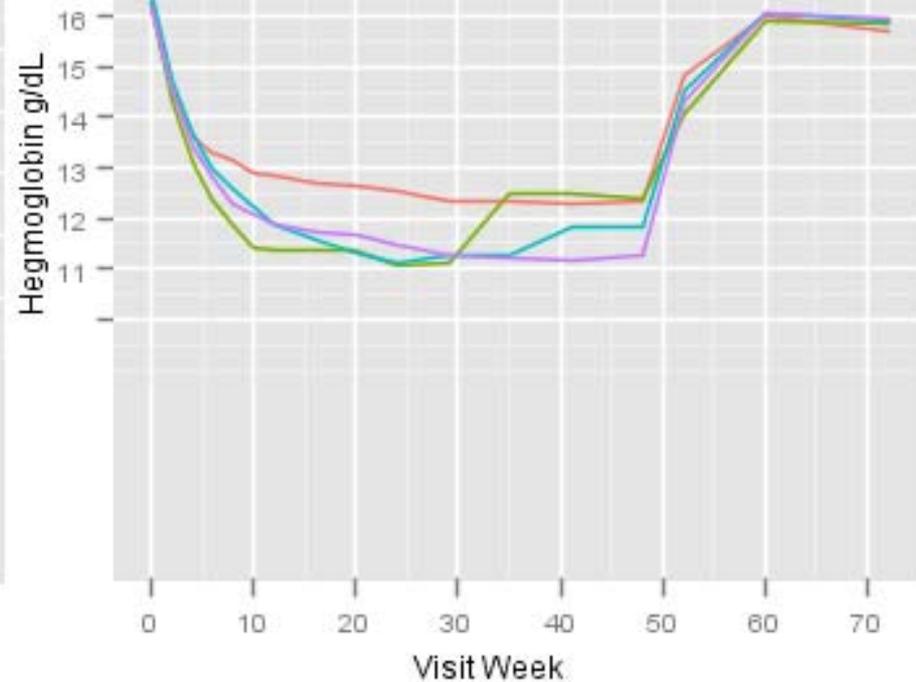
Mean Decline in Hgb by Treatment Arm and Visit



Baseline Hgb ≤ 14



Baseline Hgb ≥ 16

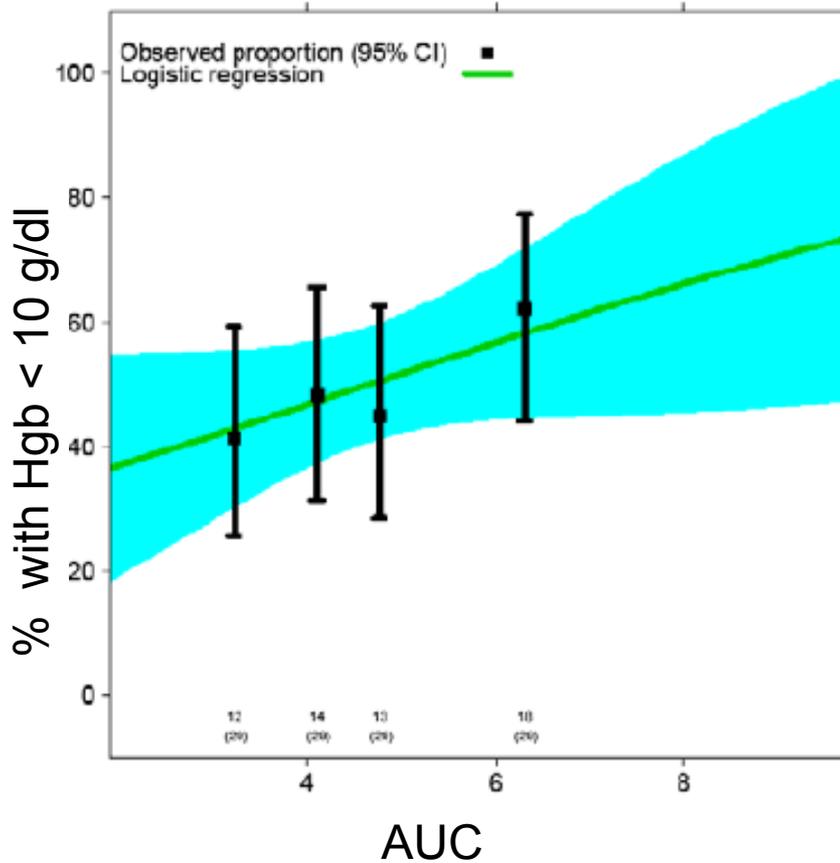


Treatment Group

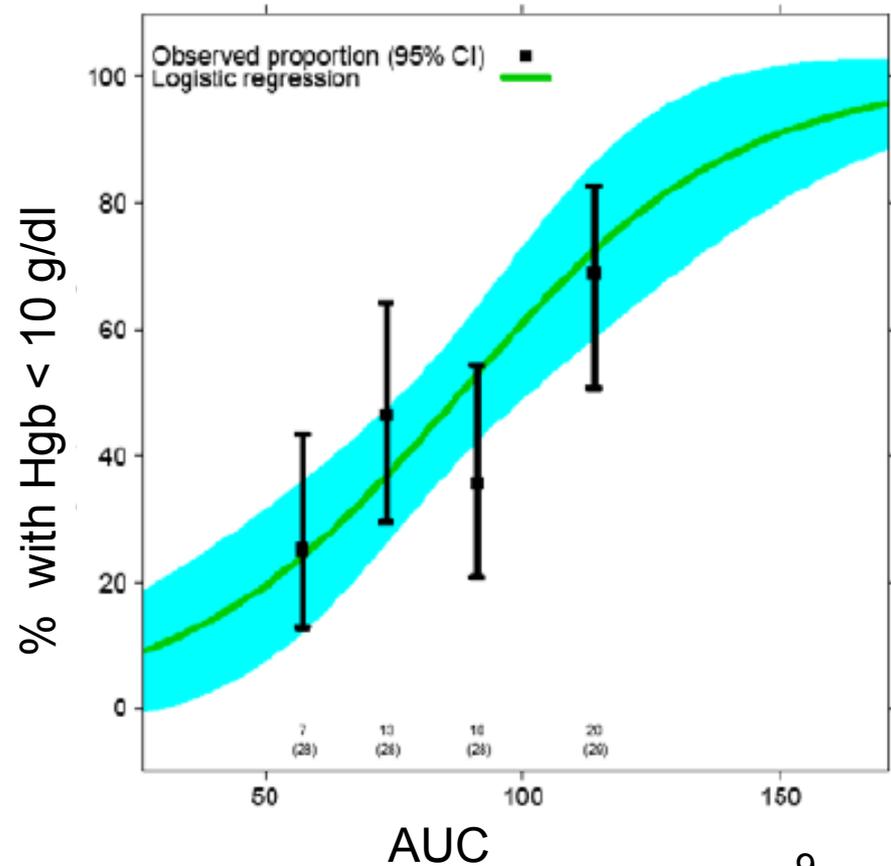
- Arm 1 PR 48 wk
- Arm 2 RGT BOC/PR 28/48 wk
- Arm 2 RGT BOC/PR 36/48 wk
- Arm 3 BOC/PR 48 wk

Anemia (%) by Drug Exposures

Boceprevir



Ribavirin



Duration ESA Exposure by Study Arm

P05216 + P05101 pooled

Trials allowed use of Erythropoiesis-stimulating agents (ESAs)

ESA Treatment Duration	PR N=443 n (%)	RGT N=530 n (%)	BOC/PR 48 N=527 n (%)
> 200 Days	22 (5)	25 (5) 	81 (15)
> 150 Days	33 (7)	57 (11) 	108 (20)
> 100 Days	50 (11)	112 (21) 	143 (27)

ESA Use: Potential Adverse Reactions

- ESAs are not FDA-approved for treatment of anemia in patients with chronic hepatitis C.
- ESA use in itself may potentially pose an additional safety risk, the extent of which has not yet been fully described.
- ESA use has been associated with increased incidence in thromboembolic events.
- There were a few thromboembolic events reported in these trials including a case of arterial thrombosis in one subject.
- Pure red-cell aplasia (PRCA) is a rare erythropoietin side effect, and was reported in one subject during the follow-up period.

Adverse Events which may represent Clinical Manifestations of Anemia

- Some adverse events were more common in boceprevir-treated subjects;
 - Dyspnea, exertional dyspnea, dizziness, syncope
- Other adverse events of interest were too infrequent to assess:
 - Myocardial infarction
 - Myocardial ischemia
 - Cerebrovascular accident/ischemia
- Trials were not designed to specifically assess incidence of symptoms and events associated with anemia.

Possible Clinical Manifestations of Anemia

P05216 + P05101 pooled

MedDRA Preferred Term	PR	RGT	BOC/PR
FATIGUE	257 (58%)	283 (53%)	301 (57%)
DYSPNEA/ DYSPNEA EXERTIONAL	107 (24%)	161 (30%)	169 (32%)
ASTHENIA	83 (19%)	86 (16)	108 (21%)
DIZZINESS	68 (15%)	106 (20%)	93 (18%)
CHEST PAIN	15 (3%)	16 (3%)	16 (3%)
CHEST DISCOMFORT	10 (2%)	9 (2%)	14 (3%)
MALaise	6 (1%)	15 (3%)	11 (2%)
SYNCOPE	3 (0.7%)	12 (2%)	11 (2%)

Anemia Events by Arm and Gender Phase 3 Trials

	Females n/N (%)	Males n/N (%)
All Subjects		
PR	77/179 (43)	53/264 (20)
RGT	128/203 (63)	139/327 (43)
BOC/PR 48	132/194 (68)	139/333 (42)
For Subjects with Similar Baseline Hgb (14-15 g/dL)		
BOC/PR 48	42/74 (57)	52/90 (58)

Neutropenia P05216 and P05101 Pooled

Lowest ANC on Treatment	ALL BOC/PR Arms N= 1050* n (%)	PR N= 438* n (%)
0.5 to <0.75 x 10⁹/L (Grade 3)	239 (23)	57 (13)
<0.5 x 10⁹/L (Grade 4)	71 (7)	19 (4)
Serious AE	3 subjects	0
Resulting in Drug Discontinuation	8 subjects	0

*N is the number with a post-baseline value

Severe and Life-threatening Infections in Subjects with Neutropenia

- Three subjects (all in boceprevir-containing arms), experienced severe infections within two weeks of Grade 3 and 4 neutropenia:
 - Epiglottitis (life-threatening) requiring tracheostomy
 - Upper respiratory infection resulting in hospitalization
 - Severe salmonella gastroenteritis
- Additionally, two cases of life-threatening neutropenia (both in boceprevir-treated subjects) were reported in study P03523 (Phase 2 - open label trial).
 - One subject developed multi-organ system failure due to sepsis, and the other experienced a fever of 104.5°F (a specific infection was not reported in these cases).

Thrombocytopenia P05216 and P05101 Pooled

Lowest Platelet Count on Treatment	ALL BOC/PR Arms N= 1050* n (%)	PR N= 438* n (%)
25 to <50 x 10⁹/L (Grade 3)	38 (4)	5 (1)
<25 X 10⁹/L (Grade 4)	2 (<1)	0
Serious AE	3 subjects	0
Resulting in Drug Discontinuation	4 subjects	0

*N is the number with a post-baseline value

Safety Conclusions

- The most notable safety concern is the additional decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin therapy alone.
- Boceprevir-treated subjects experienced more anemia, neutropenia, and thrombocytopenia.
- These appear to be part of an overall bone marrow suppressive effect of boceprevir.
- Anemia appeared to be managed effectively during the clinical trials and was reversible after the drug was discontinued.
- A few serious/life-threatening infections were reported.
- Close monitoring of laboratory parameters is recommended in clinical practice.



Clinical Virology

Most Frequent Treatment-emergent Substitutions in Boceprevir-treated Subjects Who Did Not Achieve SVR

Genotype 1a-Infected Subjects (n=211)		Genotype 1b-Infected Subjects (n=81)	
Common Substitutions	# (%) of Subjects	Common Substitutions	# (%) of Subjects
R155K	77 (36%)	T54A	16 (20%)
V36M	70 (33%)	T54S	14 (17%)
T54S	22 (10%)	I/V170A	12 (15%)
V36M + R155K	48 (23%)	A156S	10 (12%)
Any Substitution*	114 (54%)	Any Substitution*	39 (48%)

***One or more of the following boceprevir treatment-emergent substitutions:**

V36A, V36M, T54A, T54S, V55A, V107I, R155K, R155T, A156S, A156T, A156V, V158I, D168N, I/V170A, or I/V170T

Effect of Boceprevir Resistance-Associated Substitutions Detected at Baseline

- 40 subjects (4.5% of non-VF-censored, boceprevir-treated subjects) had 1 or more of the following major boceprevir treatment-emergent substitutions detected as baseline polymorphisms: **V36M, T54A, T54S, V55A, or R155K**

Boceprevir Treated Subjects (Pooled P05216+P05101)	SVR Rate According to HCV RNA Decline At Treatment Week 4		
	<2 log ₁₀ IU/mL	≥2 log ₁₀ IU/mL	All Subjects
With Baseline Resistance Substitution(s)	3/14 (21%)	25/26 (96%)	28/40 (70%)
Without Baseline Resistance Substitution(s)	238/434 (55%)	376/408 (92%)	614/842 (73%)

Possible effect on boceprevir efficacy among subjects with a relatively poor virologic response to Peg-IFNα/RBV based on lead-in period.

Persistence of Boceprevir Resistance-Associated Substitutions

- Long-term follow-up analysis of Subjects from Phase 2 boceprevir trials who:
 - Did not achieve SVR, and
 - Had one or more boceprevir treatment-emergent substitutions associated with treatment failure

Tx-emergent Substitution	% of Subjects with Detectable Substitution > 2.5 Follow-up Years
T54S	19% (14/73)
R155K	19% (13/67)
V36M	2% (1/49)
Any*	25% (26/104)
*From the following list: V36M, T54A, T54S, V55A, R155K, R155T, A156S, V158I or I/V170A	

(Note: Results based on population-based sequencing)



Efficacy Results *and* Issues

Treatment Response as described in FDA Draft HCV Guidance

Naïve: received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

Null Responder: less than $2 \log_{10}$ reduction in HCV RNA at week 12 of a Peg Interferon/RBV

Partial Responder: greater than or equal to $2 \log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a Peg Interferon/RBV

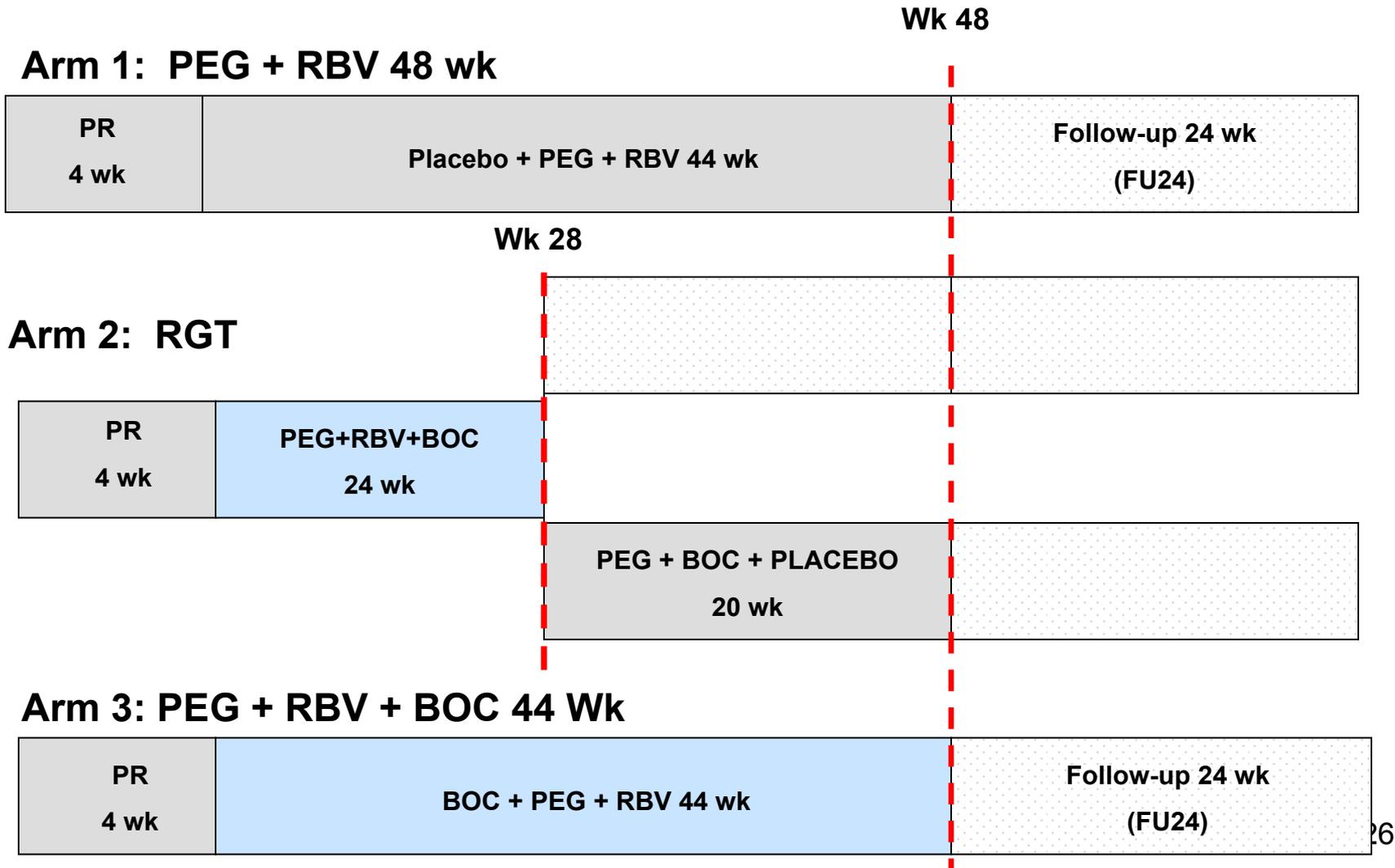
Responder Relapser: HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up

Applicant's term "non-responders" includes partial responders but does not include null responders as defined above.



Efficacy: Treatment-Naive

Trial design: P05216 (Treatment-Naive)



Primary Efficacy Results (FAS) P05216 – Treatment-Naïve Trial

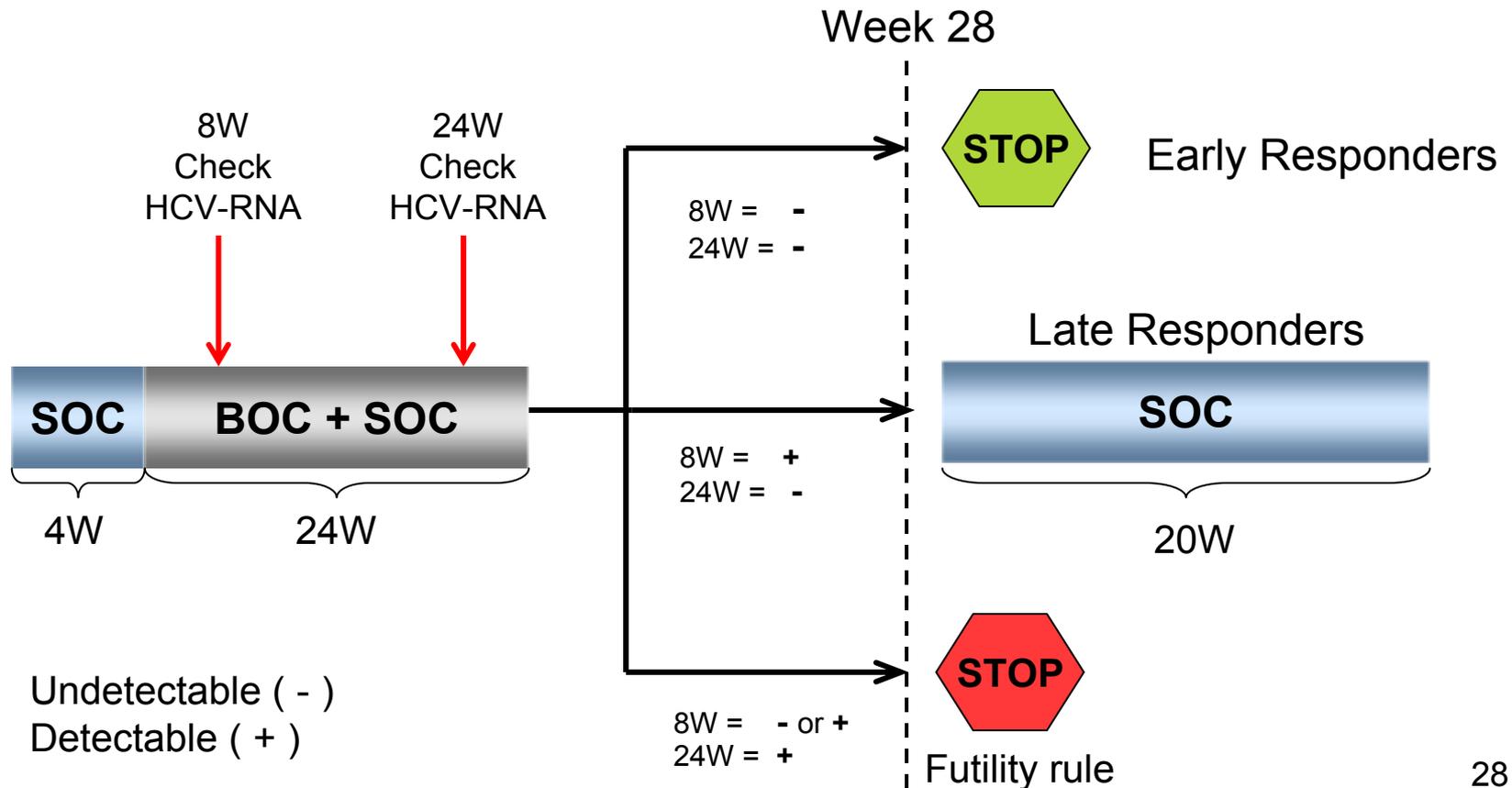
Study Cohorts	Arm 1 PR48 (Control)	Arm 2 - RGT BOC/PR	Arm 3 BOC/PR48
Cohort 1 Plus Cohort 2			
SVR % (n/N)	38 (138/363)	63 (233/368)	66 (242/366)
Relapse % (n/N)	22 (39/176)	9 (24/257)	9 (24/265)
Cohort 1 (non-Black)			
SVR % (n/N)	41 (126/311)	67 (211/316)	69 (213/311)
Relapse % (n/N)	23 (37/162)	9 (21/232)	8 (18/230)
Cohort 2 (Black)			
SVR % (n/N)	23 (12/52)	42 (22/52)	53 (29/55)
Relapse % (n/N)	14 (2/14)	12 (3/25)	17 (6/35)

Full analysis set (FAS) - all randomized subjects who received at least one dose of any study drug
SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment (EOT).

HCV RNA imputed from follow-up Week 12 if Week 24 data was missing.

Virologic Relapse= undetectable HCV RNA at EOT and HCV RNA > 25 IU/mL at end of follow-up.

Response Guided Therapy Treatment-Naïve Trial (P05216)



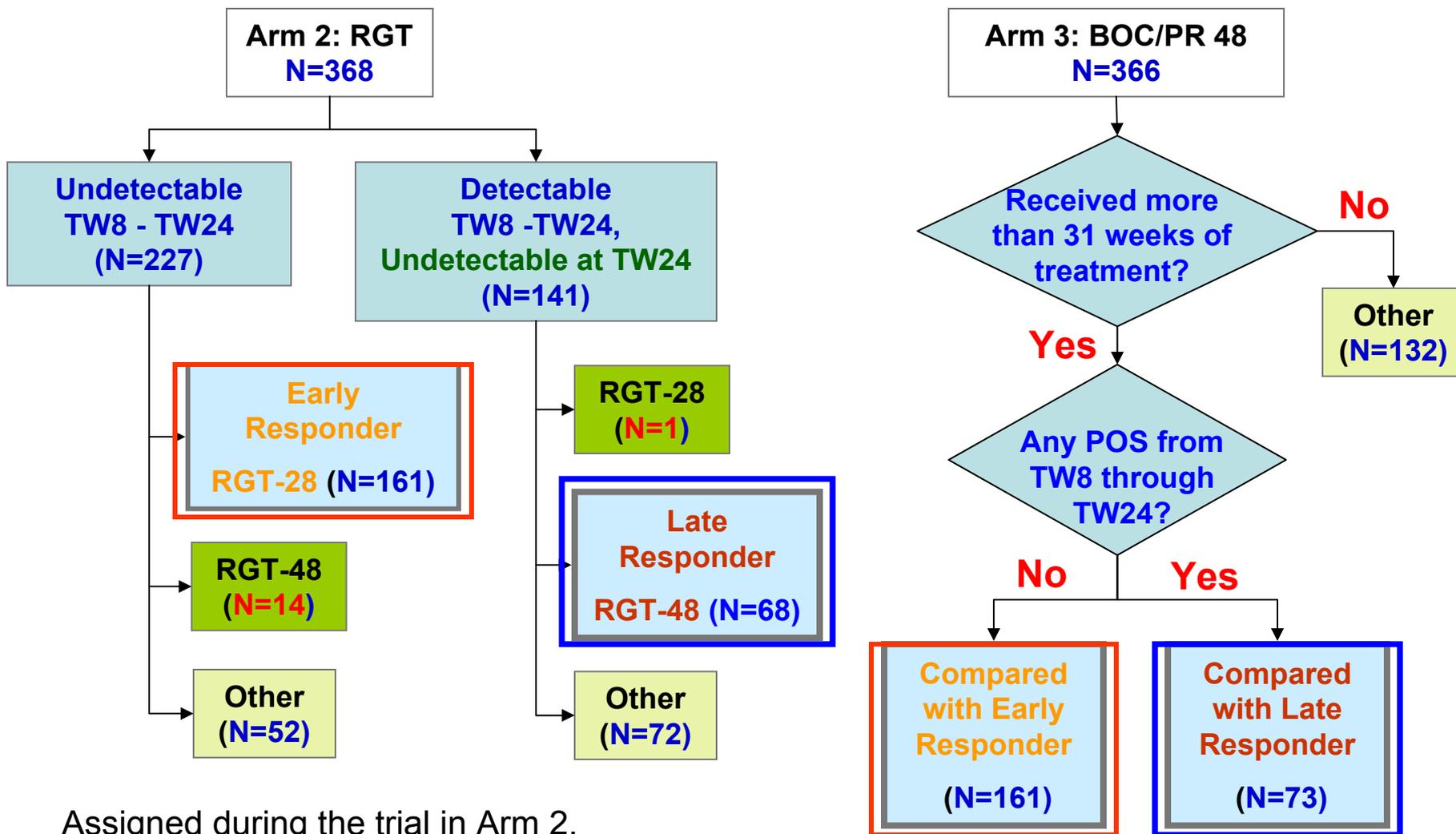
P05216 (TN) – RGT vs. BOC/PR48

Early Responders: SVR is similar in RGT and BOC/PR48

Late Responders: SVR differs between RGT and BOC/PR48

SVR	Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 (BOC48) SVR n/N (%)	Δ SVR (Arm 2-Arm 3) [95% CI of two 1-sided]
Cohort 1 + Cohort 2	Overall	233/268 (63)	242/366 (66)	-2.8 [-9.8, 4.1]
	Early Responders	156/161 (97)	155/161 (96)	0.6 [-3.8, 5.2]
	Late Responders	45/68 (66)	55/73 (75)	-9.2 [-24.4, 6.3]

P05216 (TN) – RGT vs. BOC/PR48



Assigned during the trial in Arm 2.

The visit window for TW28 is (26, 31] weeks.

Post-hoc assignment in Arm 3.

P05216 (TN) – RGT vs. BOC/PR48

Early Responders: SVR is similar in RGT and BOC/PR48

Late Responders: SVR differs between RGT and BOC/PR48

SVR	Virologic Response	Arm 2 (RGT) SVR n/N (%)	Arm 3 (BOC48) SVR n/N (%)	Δ SVR (Arm 2-Arm 3) [95% CI of two 1-sided]
Cohort 1 + Cohort 2	Overall	233/268 (63)	242/366 (66)	-2.8 [-9.8, 4.1]
	Early Responders	156/161 (97)	155/161 (96)	0.6 [-3.8, 5.2]
	Late Responders	45/68 (66)	55/73 (75)	-9.2 [-24.4, 6.3]



Efficacy: Treatment-Experienced

Trial Design: P05101 (Treatment-Experienced)

Wk 48

Arm 1: PEG + RBV 48 wk



Wk 36

Arm 2 (RGT)



Arm 3

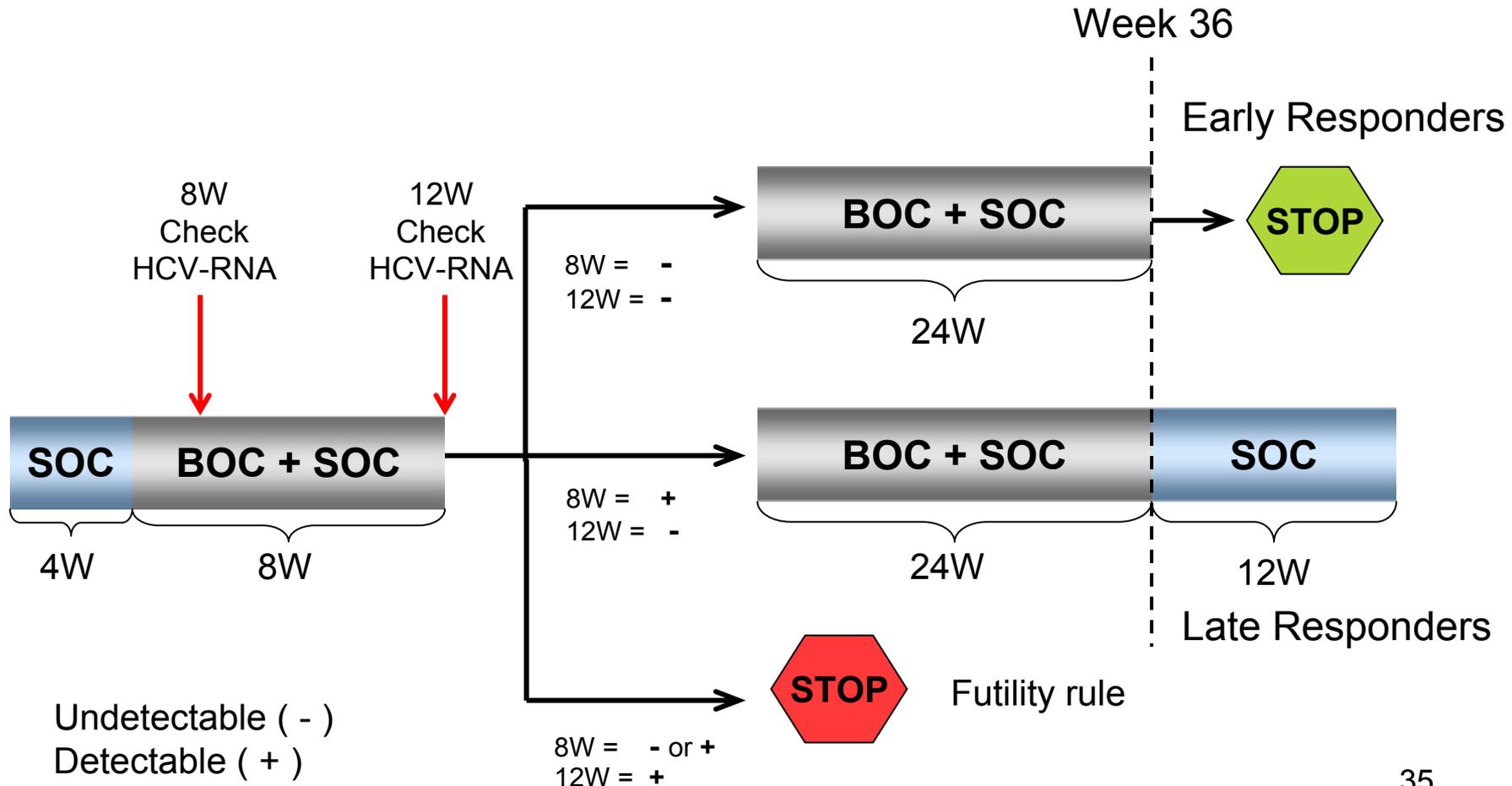


Primary efficacy Results (P05101-FAS) Treatment-Experienced

Efficacy Parameter	Arm 1 PR48 (Control)	Arm 2 RGT BOC/PR	Arm 3 BOC/PR48
SVR % (n/N)	23 (18/80)	59 (96/162)	66 (107/161)
Relapse % (n/N)	28 (7/25)	14 (16/111)	12 (14/121)
Previous Treatment Response			
Never Negative (Partial Responders)	7 (2/29)	40 (23/57)	52 (30/58)
Some Negative (Relapsers)	31 (16/51)	70 (73/105)	75 (77/103)

Full analysis set (FAS) - all randomized subjects who received at least one dose of any study drug
 SVR= sustained virologic response (HCV RNA < 25 IU/mL) at 24 weeks after the end of treatment (EOT).
 HCV RNA imputed from follow-up Week 12 if Week 24 data was missing.
 Virologic Relapse= undetectable HCV RNA at EOT and HCV RNA > 25 IU/mL at end of follow-up.

Response Guided Therapy for Treatment Experienced Trial (P05101)



P05101 (TE) – RGT vs. BOC/PR48

Virologic Response (TW 8 and TW 12)	Arm 2 RGT SVR % (n/N)	Arm 3 BOC/PR48 SVR % (n/N)	Treatment Difference Arm 2-3 [95% 2-sided CI]
Overall	59 (96/162)	66 (107/161)	-7.2 [-17.7, 3.5]
Early Responders	91 (62/68)	97 (68/70)	-6.0 [-15.6, 2.2]
Late Responders	79 (27/34)	73 (29/40)	6.9 [-14.0, 26.7]



Efficacy: Subgroup

Fibrosis/Cirrhosis



Efficacy: Fibrosis/Cirrhosis

	Arm 1 PR 48 n/N (%)	Arm 2 RGT n/N (%)	Arm 3 BOC/PR 48 n/N (%)
P05216 (Naive)			
<i>All Subjects</i>	138/363 (38)	233/368 (63)	242/366 (66)
Metavir Fibrosis Score			
Group F 0/1/2	124/328 (38)	213/319 (67)	211/313 (67)
Group F 3/4	9/24 (38)	14/34 (41) 	22/42 (52)
Cirrhosis:			
NO	127/339 (38)	222/337 (66)	223/331 (67)
YES	6/13 (46)	5/16 (31) 	10/24 (42)
P05101 (Experienced)			
<i>All Subjects</i>	18/80 (23)	96/162(59)	107/161(67)
Metavir Fibrosis Score			
Group 0/1/2	14/61 (23)	78/117 (67)	81/119 (68)
Group 3/4	3/15 (20)	14/32 (44) 	21/31 (68)
Cirrhosis:			
NO	17/66 (26)	86/132 (65)	85/128 (66) ₃₈
YES	0/10 (0)	6/17 (35) 	17/22 (77)

Efficacy Conclusions

- Overall, in the treatment-naïve subjects (P05216), SVR was 63% - 66% in boceprevir-containing arms versus 38% in the control arm.
- Overall, in the treatment-failure subjects (P05101), SVR was 59% - 66% in boceprevir-containing arms versus 21% in the control arm.
- The treatment difference was substantially significant and robust for each trial based on the primary efficacy endpoint.
- Relapse rates were also lower in boceprevir-treated subjects.
- Efficacy of boceprevir was demonstrated in subjects regardless of race (non-black and black).
- Response-guided therapy approach in early responders provides a potential shorter duration of therapy.

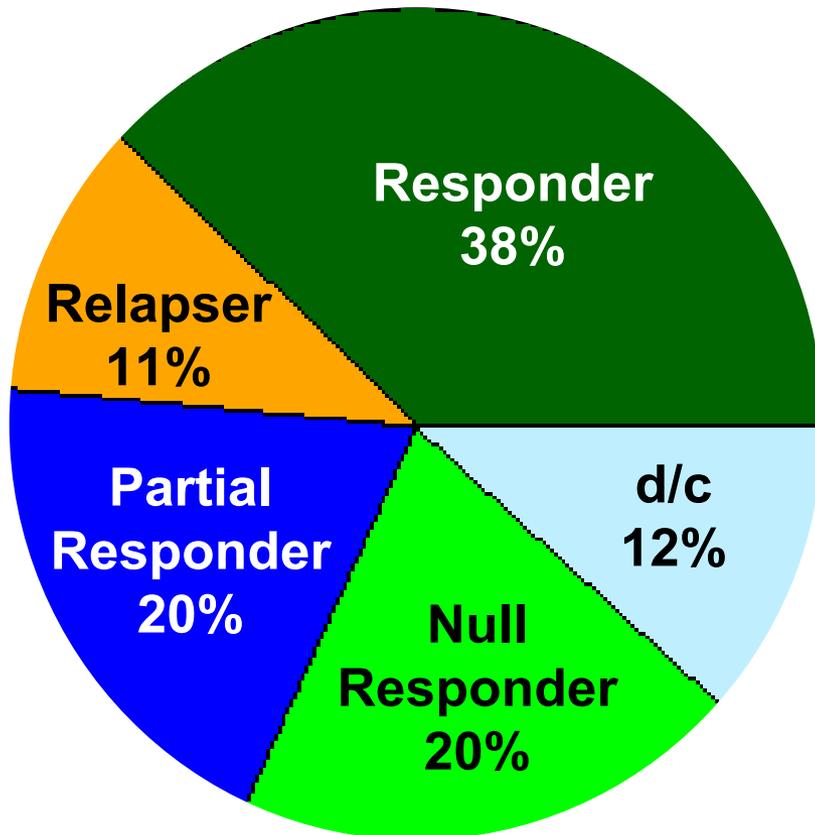
Boceprevir Treatment Duration Treatment-Experienced (TE) Subjects

	Treatment-Experienced	
	Prior Relapser/ Prior Partial Responder	Prior Null Responder
Early Responder	PR4/BOC+PR32	Question 3 to AC?
Late Responder	PR4/BOC+PR32/PR12	

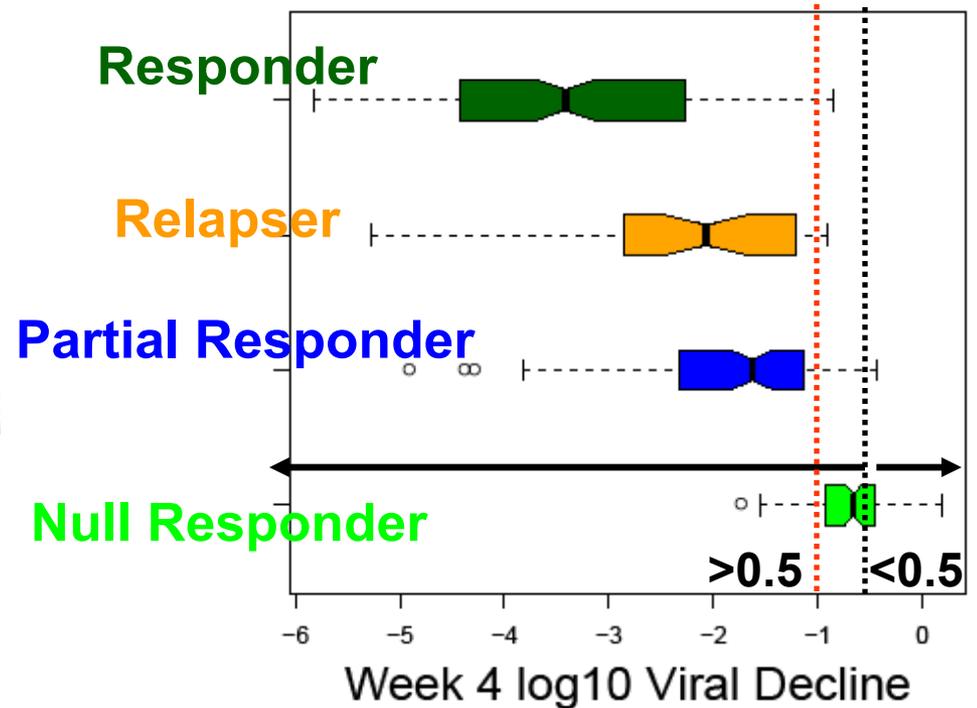
Question 3 to AC: Is there Evidence for Use of Boceprevir in Combination with PR in **Prior Null Responders?**

Null Responders can be identified based on Week 4 PR response (<0.5 or <1 log decline) in TN subjects

TN P05216: PR Treatment Outcome



Week 4 Log Decline in Viral Load to PR



Higher SVR in Subjects with <0.5 or <1 log Week 4 PR response with Boceprevir Treatment Compared to PR Treatment

Week 4 Viral load decline	% null responders, (n/N)	Observed SVR in PR TN Arm	Observed SVR in Boceprevir TN Arms	
			RGT	PR4/BOC+PR44
<1.0	69% (57/83)	4%	28%	38%
<0.5	88% (22/25)	0%	28%	30%

- <1.0 log₁₀ decline includes subjects who are **not null responders** and may **over estimate SVR**
- <0.5 log₁₀ decline includes **predominantly null responders** and provides a **more conservative estimate** for SVR

Question 3 to AC

Is there Evidence for Use of Boceprevir in Combination with PR in **Prior Null Responders**?

- Data from subjects with **<0.5 or <1 log₁₀ HCV RNA** decline informs about drug effect in **null responders**
- Treatment with Boceprevir improves SVR in null responders.
- Null responders may benefit from longer duration of triple therapy

Boceprevir Treatment Duration Treatment-Experienced (TE) Subjects

	Treatment-Experienced	
	Prior Relapser/ Prior Partial Responder	Prior Null Responder
Early Responder	PR4/BOC+PR32	PR4/BOC+PR44
Late Responder	PR4/BOC+PR32/PR12	

Boceprevir Treatment Duration Treatment-Naive (TN) Subjects

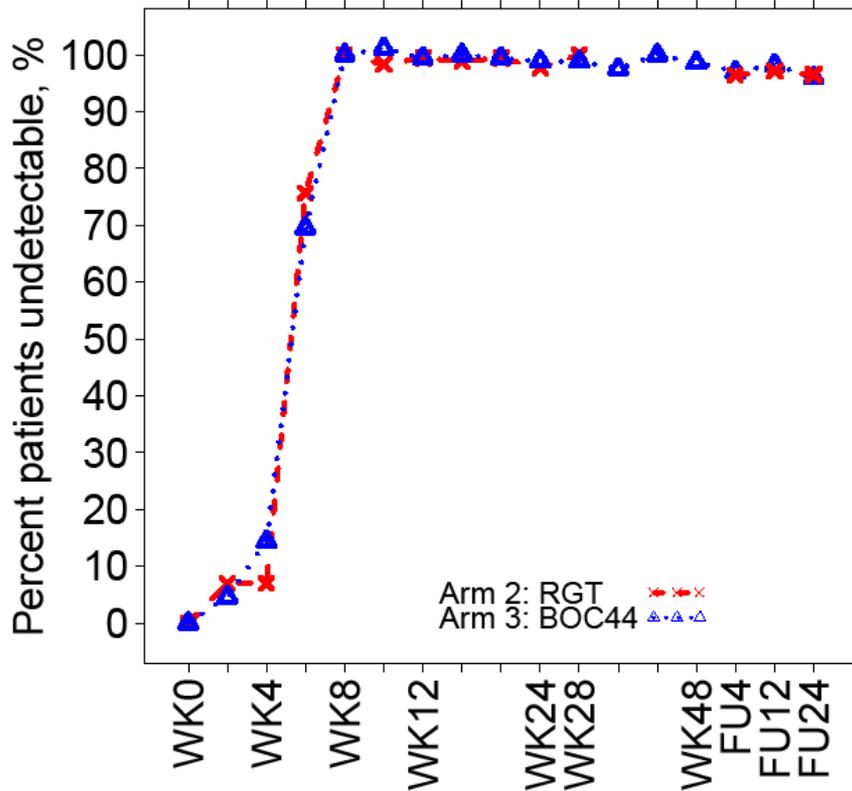
	Treatment-Naive
Early Responder	PR4/BOC+PR24
Late Responder	Question 4a to AC?

Question 4a to AC: Should **Treatment-Naïve (TN) Late Responders** Receive a Longer Duration of Boceprevir Treatment?

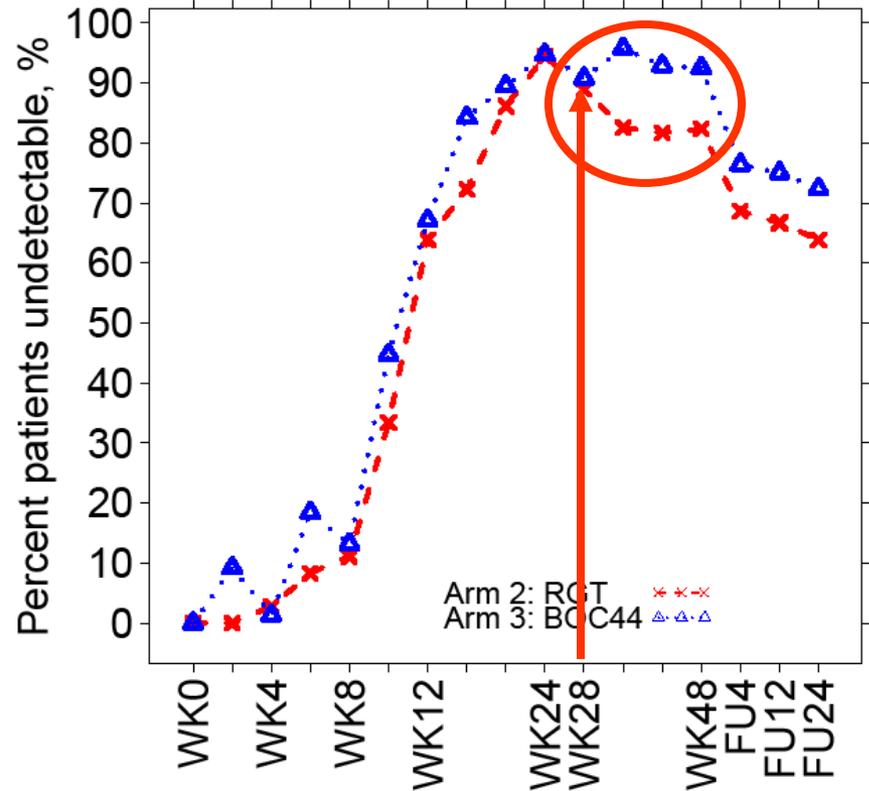
Numerical Difference in SVR for TN Late Responders between RGT (BOC 24) and BOC44

P05216	RGT SVR n/N (%)	BOC44 SVR n/N (%)
	PR4/BOC+PR24	PR4/BOC+PR44
Early Responders	156/161 (97)	155/161 (96)
	PR4/BOC+PR24/PR20	PR4/BOC+PR44
Late Responders	45/68 (66)	55/73 (75)

24 Weeks of Boceprevir is Suboptimal for TN Late Responders



Treatment-Naïve:
Early Responder



Treatment-Naïve:
Late Responder

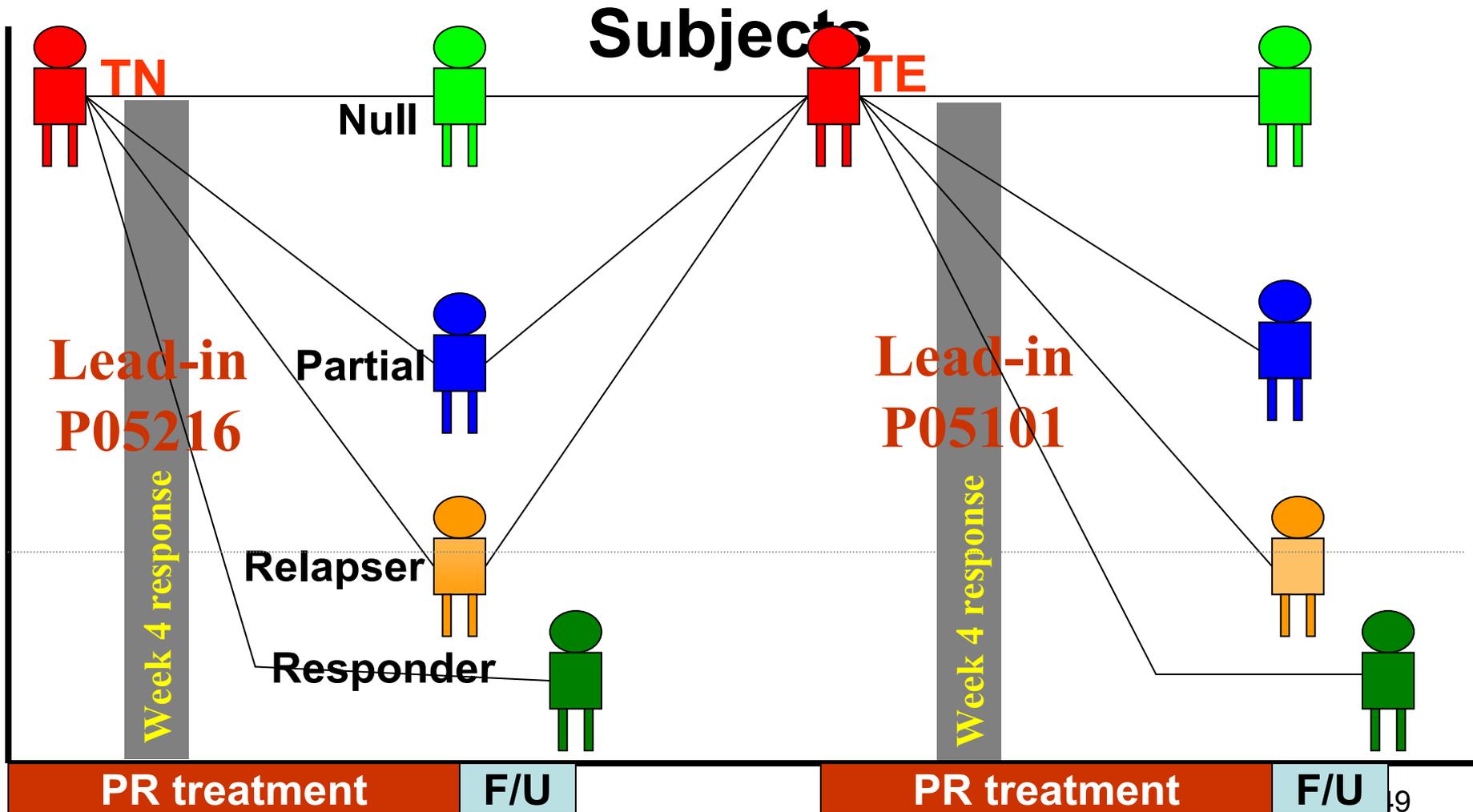
Question 4a to AC

Should **Treatment-Naïve (TN) Late Responders** Receive a Longer Duration of Boceprevir Treatment?

Option 1	Treatment-Naive
Early Responder	PR4 /BOC+PR24
Late Responder	PR4 /BOC+PR44

•Evidence from TN late responder treatment arms

TN Population Contains *future* Relapser, Partial and Null Responder



Similar Virologic Response at Week 4 with First or Second PR treatment

Population	Study	Week 4 Decline in log ₁₀ Viral Load
		Mean
<i>TN Future</i> Relapse	P05216	2.1
TE Prior Relapse	P05101	2.2
<i>TN Future</i> Partial	P05216	1.6
TE Prior Partial	P05101	1.2

- The range of week 4 response (not just mean) is also similar for respective comparisons

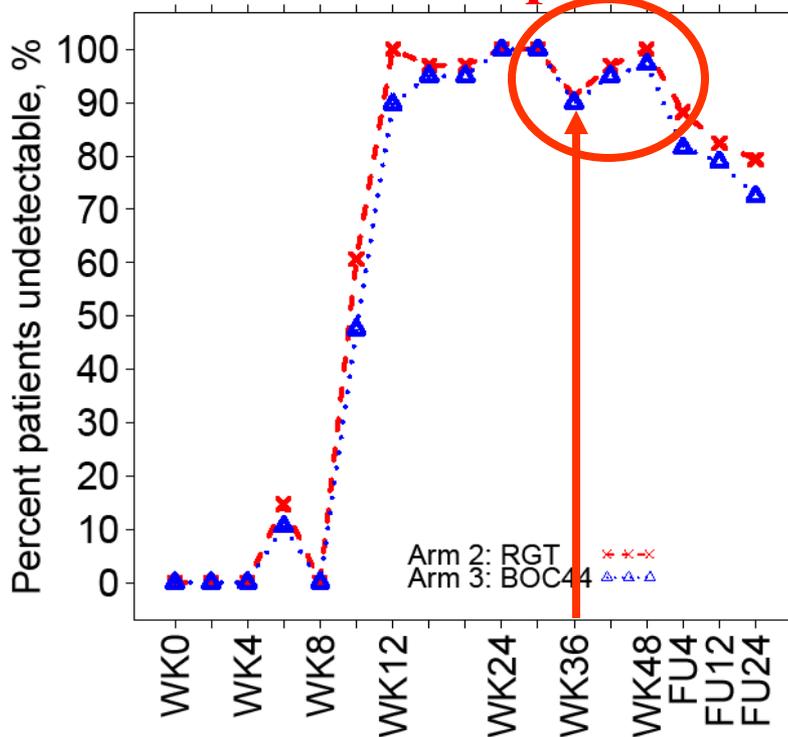
Similar Virologic Response at Week 4 for Late Responders and Future PR Treatment Failures

Population	Study	Week 4 Decline in log ₁₀ Viral Load
		Mean
<i>TN Future Relapse</i>	P05216	2.1
<i>TN Future Partial</i>	P05216	1.6
<i>TN Future Null</i>	P05216	0.7
TN RGT Late Responder	P05216	1.0
TE RGT Late Responder	P05101	1.3

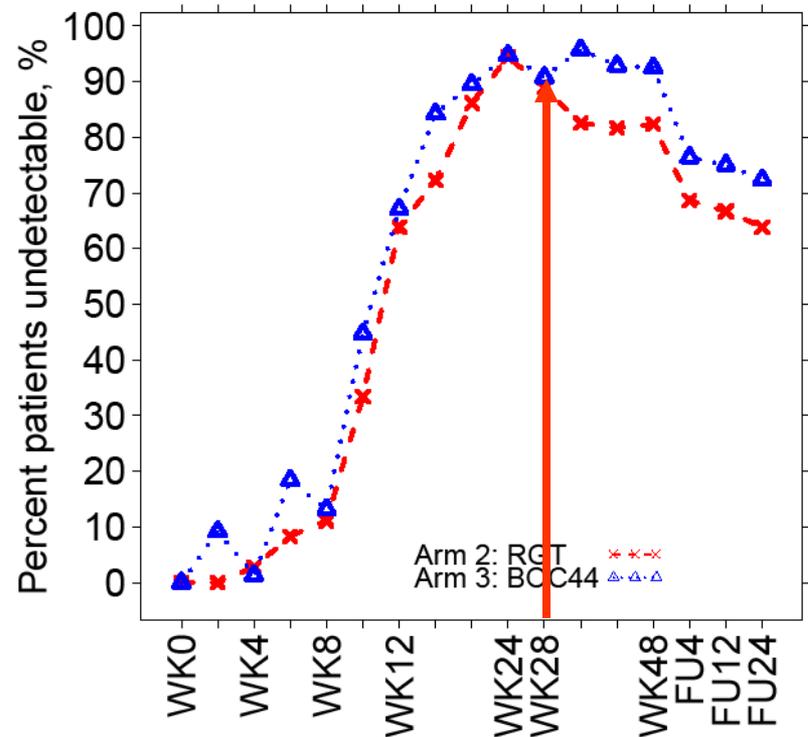
- P05101 did not include null responders

32 Weeks of Boceprevir may be Sufficient in TN Late Responders

Treatment-Experienced



Treatment-Naïve



Study and Treatment Group	Arm 2: RGT (PR4/BOC-PR32/PR12) SVR n/N (%)	Arm 3: BOC44 (PR4/BOC-PR44) SVR n/N (%)
P05101 Late Responders	27/34 (79)	29/40 (73)

Question 4a to AC

Should **Treatment-Naïve (TN) Late Responders** Receive a Longer Duration of Boceprevir Treatment?

Option 2	Treatment-Naive
Early Responder	PR4 /BOC+PR24
Late Responder	PR4 /BOC+PR32/PR12

- Evidence from TE late responder treatment arms
- Bridging information between TN and TE late responders

Boceprevir Treatment Duration for TN and TE Subjects

	Treatment naïve	Treatment-Experienced	
		Relapser/ Partial Responder	Null Responder
Early Responder	PR4/BOC+PR24	PR4/BOC+PR32	
Late Responder	PR4/BOC+PR44 OR PR4/BOC+PR32/PR12	PR4/BOC+PR32/PR12	PR4/BOC+PR44

- **Currently posed TN late responder treatment options may result in suboptimal treatment duration in a subset of subjects**