Review of FDA LOD/LLOQ Analyses of Boceprevir and Telaprevir

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Disclaimer

The views expressed in these slides are those of the presenter and do not necessarily represent official policy of the Food and Drug and Administration.

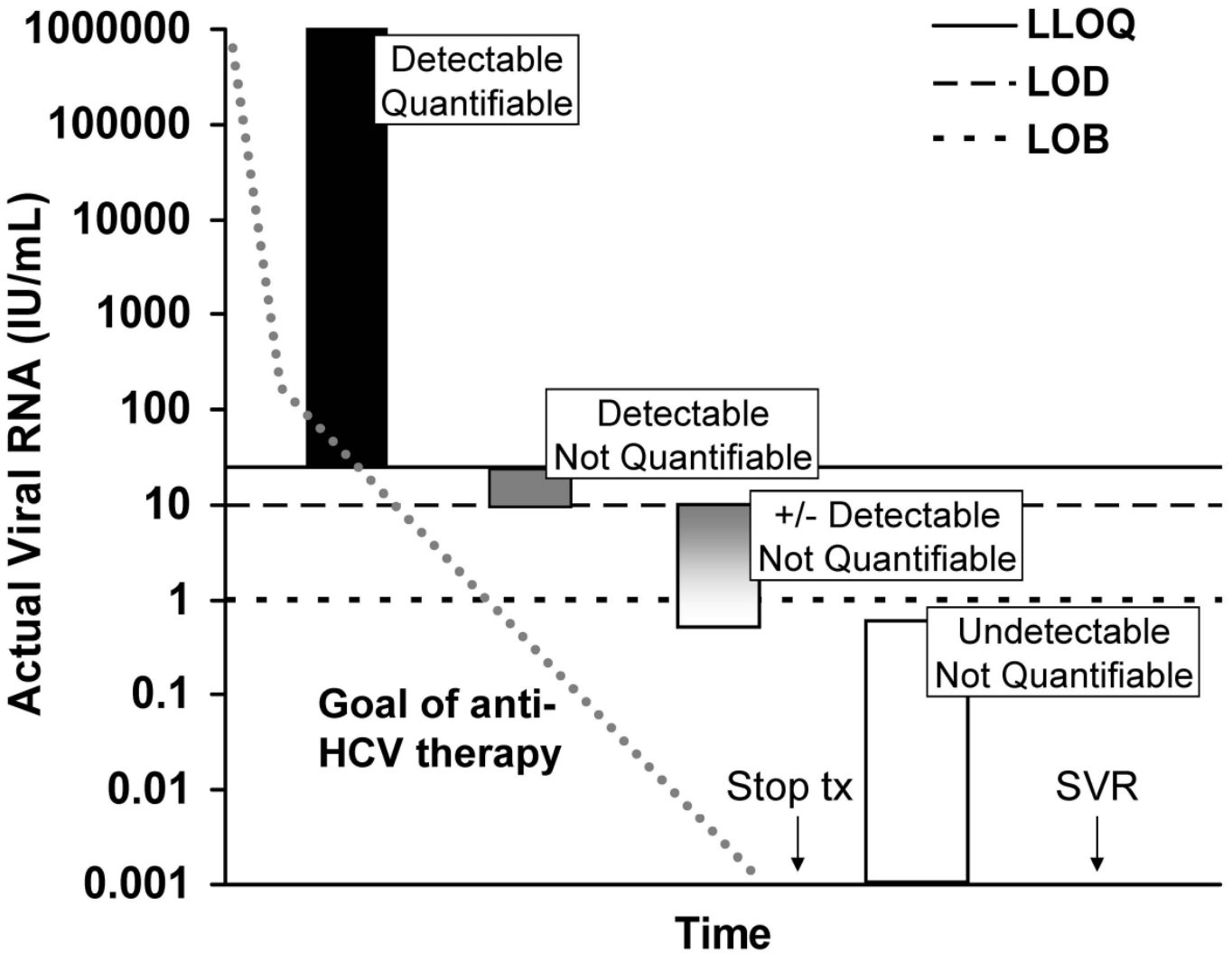
Reference

Harrington P.R., Zeng W., Naeger L.K. Clinical Relevance of Detectable but Not Quantifiable Hepatitis C Virus RNA during Boceprevir or Telaprevir Treatment. *Hepatology.* In press.

Some Terminology

Clinicians/Protocols	**Assay Developers**
Undetectable or <LOD	HCV RNA (i.e., "Target") Not Detected
Detectable	HCV RNA Detected
Quantifiable	HCV RNA Detected, and ≥LLOQ
Detectable/Not Quantifiable or Detectable/BLOQ	HCV RNA Detected, but <LLOQ

"HCV RNA Detected" is frequently referred to as ">LOD". This is not technically accurate.


LLOQ
LOD
LOB
Actual Viral RNA (IU/mL)
1000000
100000
10000
1000
100
10
1
0.1
0.01
0.001
Detectable
Quantifiable
Detectable
Not Quantifiable
+/- Detectable
Not Quantifiable
Undetectable
Not Quantifiable
Goal of anti-
HCV therapy
Stop tx
SVR
Time

Summary

Are Detectable/BLOQ and Undetectable HCV RNA levels qualitatively different?

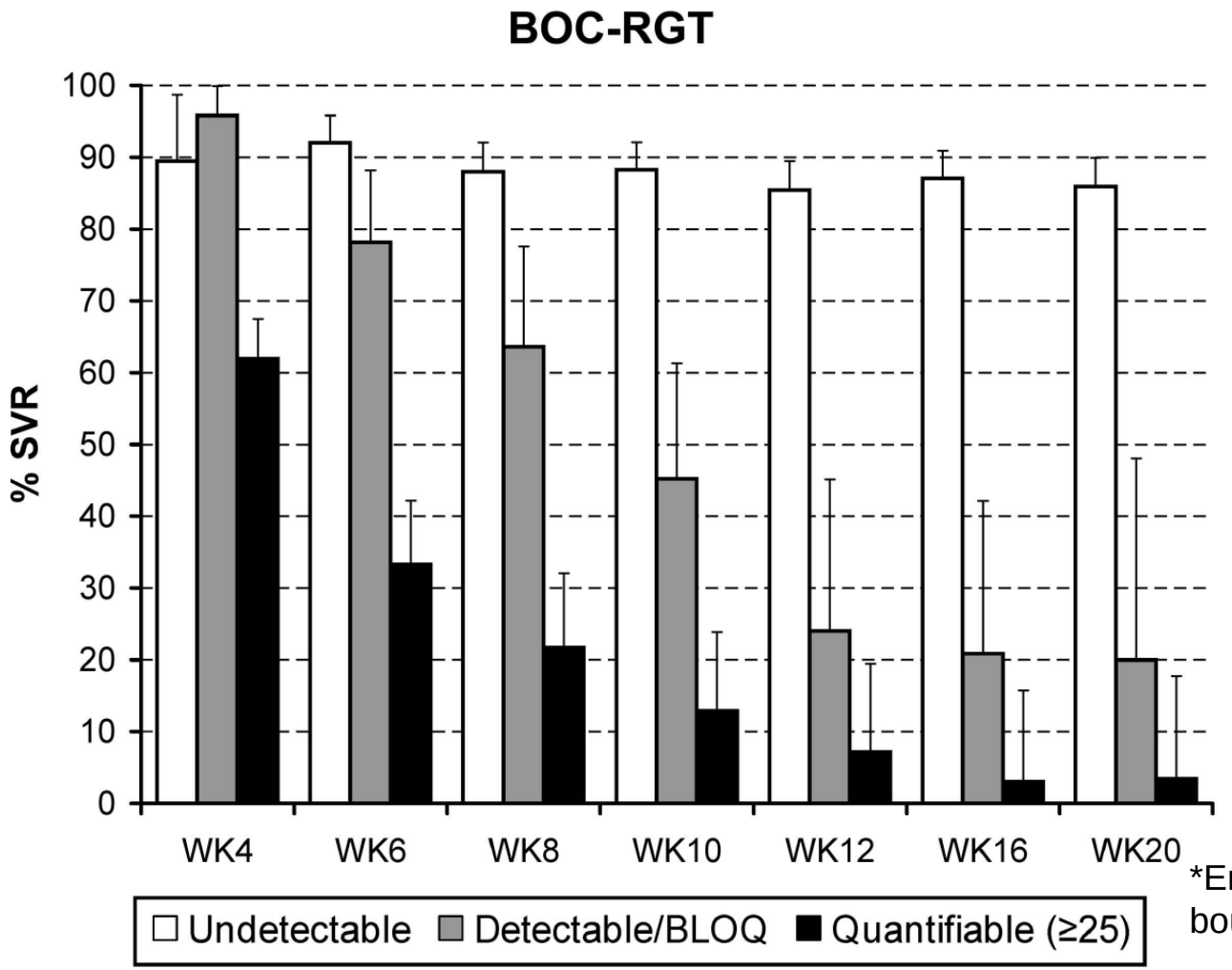
Yes, on average, based on the following analyses:

- 3 different, large phase 3 clinical trials
- 3 smaller phase 2 clinical trials
- 4 different treatment regimens (BOC+PR, TVR+PR w/o PR lead-in, TVR+PR with PR lead-in, PR alone)
- 2 assay vendors with variability in assay performance (differences based on Vendor B less striking, but same trend)
- 2 independent FDA Clinical Virology reviews

Is Detectable/Undetectable HCV RNA a perfect cutoff for on-treatment RGT decision making?

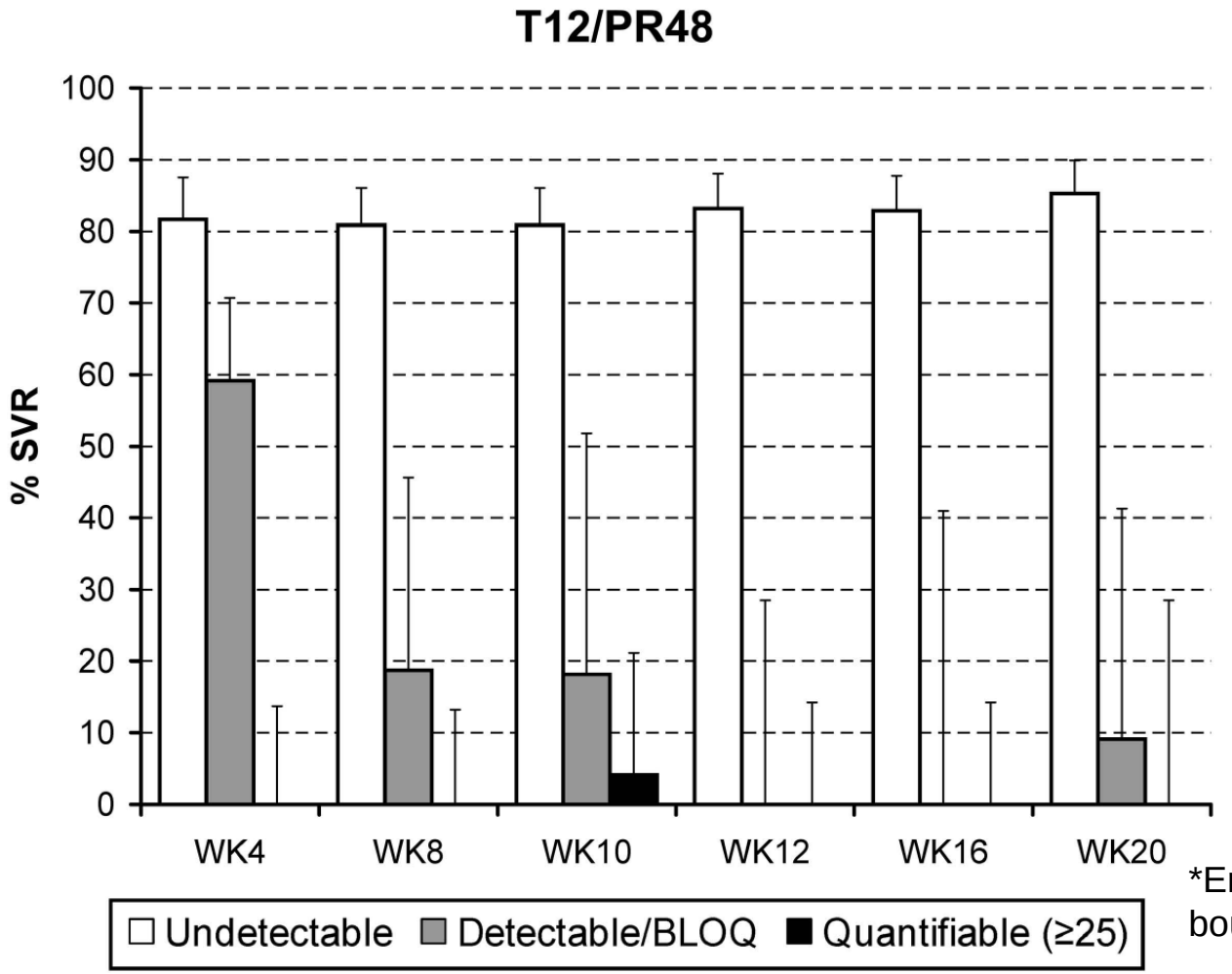
No

SVR According to On-Tx HCV RNA Status:
Boceprevir SPRINT-2 Trial (P/R-naïve)



*Error bars: upper bound of 95% CI

SVR According to On-Tx HCV RNA Status:
Telaprevir REALIZE Trial (P/R Experienced)



*Error bars: upper bound of 95% CI

Phase 2 Studies

Study, Population, and Treatment Arm	SVR Rate	Relapse Rate
Boceprevir Study P03523 (SPRINT-1)		
Detectable/BLOQ HCV RNA at Week 8		
PR for 4 Weeks, Boceprevir/PR for 24 Weeks	5/13 (38%)	5/10 (50%)
PR for 4 Weeks, Boceprevir/PR for 44 Weeks	9/12 (75%)	0/9 (0%)
Undetectable HCV RNA at Week 8		
PR for 4 Weeks, Boceprevir /PR for 24 Weeks	53/62 (85%)	4/57 (7%)
PR for 4 Weeks, Boceprevir /PR for 44 Weeks	62/66 (94%)	0/62 (0%)
Pooled Telaprevir Studies 104, 104EU (PROVE 1,2)		
Detectable/BLOQ HCV RNA at Week 4		
Telaprevir/PR for 12 weeks, PR for 12 Weeks	6/15 (40%)	4/9 (44%)
Telaprevir/PR for 12 weeks, PR for 36 Weeks	4/7 (57%)	2/6 (33%)
Undetectable HCV RNA at Week 4		
Telaprevir/PR for 12 weeks, PR for 12 Weeks	89/120 (74%)	6/88 (7%)
Telaprevir/PR for 12 weeks, PR for 36 Weeks	49/64 (77%)	0/44 (0%)

Labels

- FDA Reviewer's Responsibility:
  - Ensure the label accurately reflects how the drug was studied
  - Some discretion if data analyses support divergence from study protocols
  - *Analyses did not support divergence from HCV RNA cutoffs in study protocols for RGT decision making*
- *(For RGT decision making)…"a confirmed 'detectable but below limit of quantification' HCV-RNA result should not be considered equivalent to an 'undetectable' HCV-RNA result"*

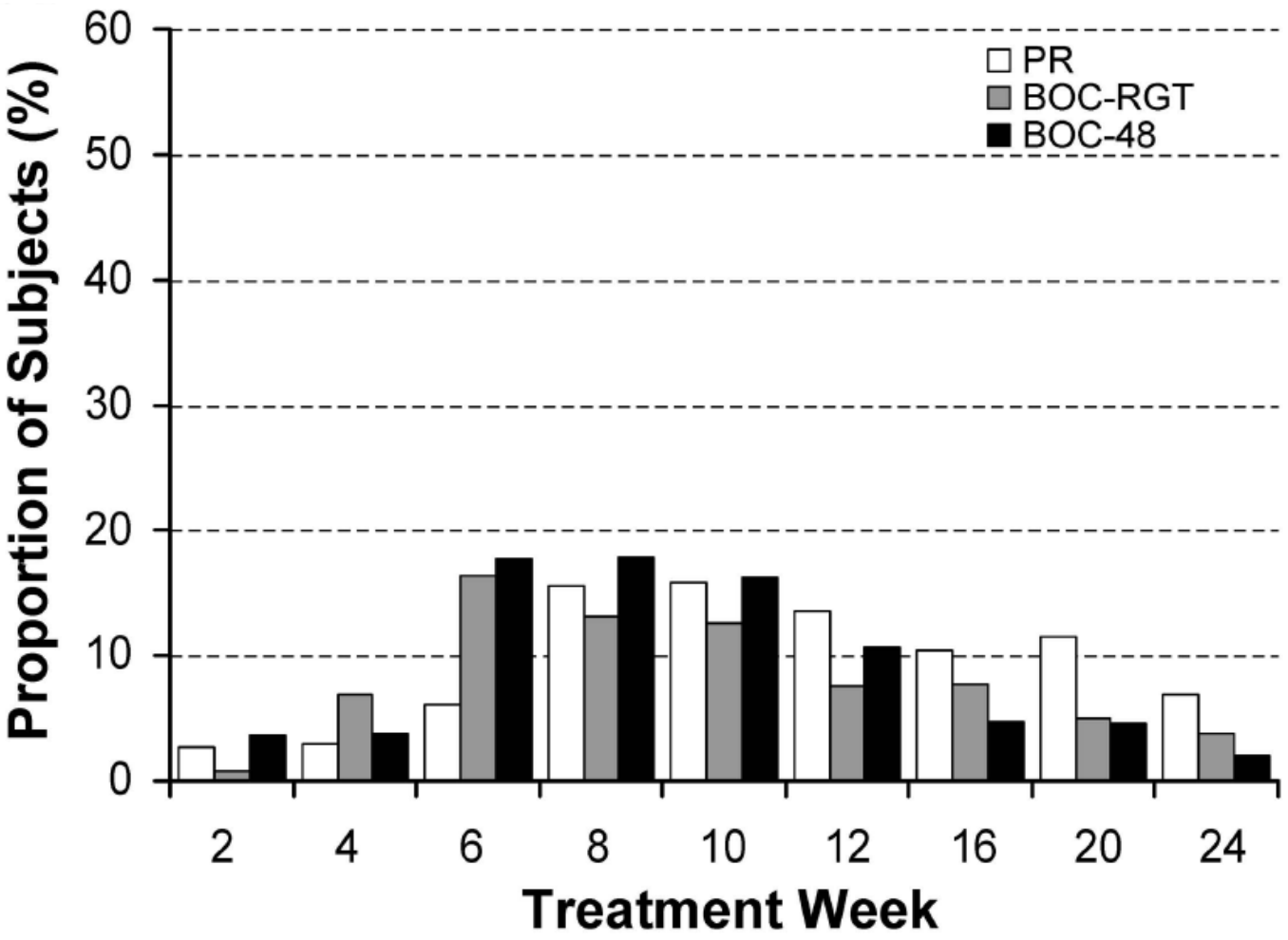
  ("confirmed" added to support retesting at individual discretion)

Going Forward

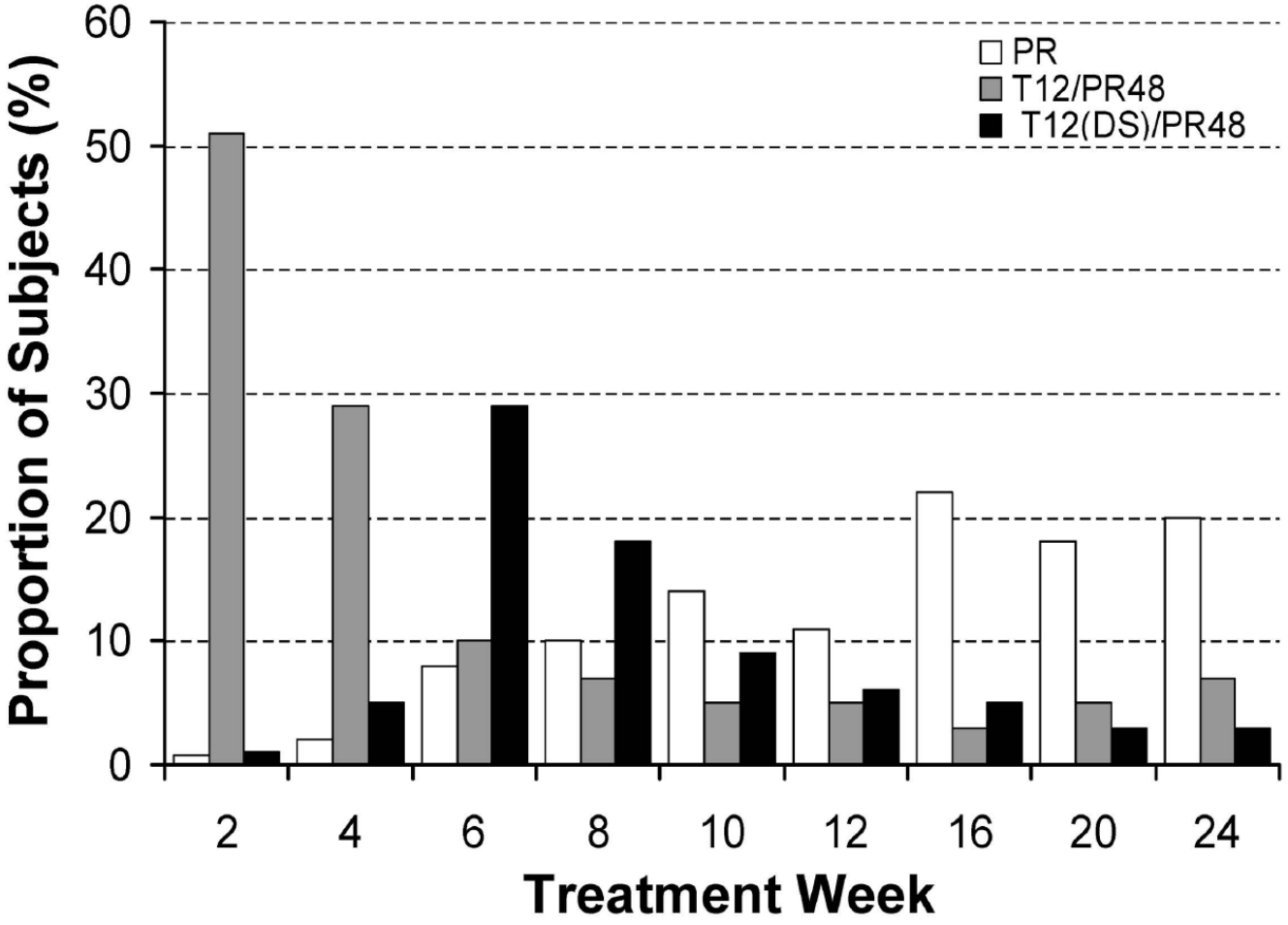
- We support efforts by HCV DrAG or other consortia to provide data-driven guidance and education for care providers using currently approved drugs
- We have recommended sponsors explore using LLOQ (or other specific IU/mL cutoff) for RGT decision making in Phase 2 and Phase 3 trials
- We encourage exploration of other RGT strategies/algorithms (Magnitude of early HCV RNA decline? Slope of HCV RNA decline?)
- We encourage comparative analyses of different HCV RNA assays
- **Longer term?** LOD/LLOQ not expected to be a major issue with short, fixed duration, IFN-free treatment regimens

Backup Slides

Frequency of Detected/<LLOQ HCV RNA:
Boceprevir SPRINT-2 Trial (P/R-naïve)



Frequency of Detected/<LLOQ HCV RNA:
Telaprevir REALIZE Trial (P/R-experienced)



Detectable/BLOQ as a Transition Phase