Supplementary Online Content

Poordad F, Sievert W, Mollison L, et al. Fixed-dose combination therapy with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. *JAMA*. doi:10.1001/jama.2015.3860.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Combined analysis to determine historical threshold SVR

The historical threshold SVR rate was derived from a combined analysis in subjects treated with peg-interferon/ribavirin in combination with either sofosbuvir or simeprevir.

The historical threshold based on these SVR rates is:

Treatment-naive	79%
Treatment-experienced	48%

The treatment-naive data is from the NEUTRINO trial for sofosbuvir, which demonstrated an SVR rate of 91% (95% CI 87-94%) in non-cirrhotic subjects [FDA antiviral drugs advisory committee, NDA 204671, 25 October, 2013]. Using a non-inferiority margin of 15% (in consideration for an IFN-free regimen), the threshold for non-cirrhotic subjects was calculated by subtracting the non-inferiority margin from the upper bound of the 95% CI of the point estimate (94% - 15%), which is 79%.

The prior relapse data is from trial HPC3007 for simeprevir (Forns et al. Gastroenterology 2014;146:1669-1679), and the non-responder data is from C206 study for simeprevir (FDA antiviral drugs advisory committee, NDA 205123, 24 October, 2013. Simeprevir (TMC435]).

	SVR
Treatment-naive	79%
Prior relapse	72%
Non-responder (partial, null)	62%

For treatment-experienced subjects, a composite historical threshold was used, taking into account past treatment response to interferon and RBV as relapse or non-response. Subjects who are intolerant of interferon or who previously failed DAA treatment (if allowed per protocol) have no treatment options so are assigned a historical threshold of 5%.

Calculation of the composite historical threshold for treatment-experienced subjects:

Virologic failure 67% (average of 72% SVR for relapse, 62% for null/partial), which assumes equal numbers of relapse and null/partial subjects

Interferon intolerant	5% (no treatment option)
DAA failure	5% (no treatment option)

The final composite threshold for non-cirrhotic, treatment-experienced subjects, assuming enrollment of 70% virologic failure, 20% interferon-intolerant, and 10% DAA failure, is 48%.

70% x (67% SVR) + 20% x (5% SVR) + 10% x (5% SVR) = 48%

eTable. Virologic response by time point (HCV RNA <LLOQ)

HCV RNA <LLOQ, n (%) [95% CI]	Treatment-naive N=312	Treatment-experienced N=103
Week 1	109/312 (34.9) [29.6, 40.2]	29/103 (28.2) [19.5, 36.8]
Week 2	244/312 (78.2) [73.6, 82.8]	77/103 (74.8) [66.4, 83.1]
Week 4	304/312 (97.4) [95.0, 98.9]*	100/103 (97.1) [91.7, 99.4]*
Week 6	304/312 (97.4) [95.0, 98.9]*	100/103 (97.1) [91.7, 99.4]*
Week 8	303/312 (97.1) [94.6, 98.7]*	99/103 (96.1) [90.4, 98.9]*
Week 12 (EOT)	300/312 (96.2) [93.4, 98.0]*	98/103 (95.1) [89.0, 98.4]*
Post-treatment Week 4 (SVR4)	292/312 (93.6) [90.9, 96.3]	92/103 (89.3) [83.4, 95.3]
Post-treatment Week 8 (SVR8)	284/312 (91.0) [87.9, 94.2]	91/103 (88.3) [82.2, 94.5]
Post-treatment Week 12 (SVR12)	287/312 (92.0) [89.0, 95.0]	92/103 (89.3) [83.4, 95.3]

EOT, end of treatment; LLOQ, lower limit of quantification, TD, target detected; TND, target not detected.

*Exact binomial Confidence Interval.