Supplementary Online Content


eAppendix

This supplementary material has been provided by the authors to give readers additional information about their work.
The historical threshold SVR was derived from a combined analysis in subjects treated with peg-interferon/ribavirin in combination with either sofosbuvir or simeprevir.

The final historical threshold based on these SVR rates is:

**Cirrhotic**
- Treatment-naive: 69%
- Treatment-experienced: 45%

The treatment-naive data is from the NEUTRINO trial for sofosbuvir, which demonstrated SVR rate of 91% (95% confidence interval 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% confidence interval of the point estimate (94% - 15%), which is 79%.

In the NEUTRINO trial, the SVR for cirrhotic subjects was 10% lower than for non-cirrhotic subjects (81% vs. 91%). Therefore, the historical threshold for cirrhotic subjects in AI443113 was determined by subtracting 10% from the historical threshold for non-cirrhotic subjects, which is 79%-10% = 69%.

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].

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<tr>
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<th>SVR</th>
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<tr>
<td>Treatment-naive</td>
<td>69%</td>
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<tr>
<td>Prior relapse</td>
<td>67%</td>
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<tr>
<td>Non-responder (partial, null)</td>
<td>58%</td>
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For treatment-experienced subjects, a composite historical threshold will be 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%.

Virologic failure 62.5% (average of 67% SVR for relapse, 58% for null/partial) - assumes equal number of relapse and null/partial subjects

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

The final composite threshold for cirrhotic, treatment-experienced subjects, assuming enrollment of 70% virologic failure, 20% interferon-intolerant, and 10% DAA failure, is 45%.

70% x (62.5% SVR) + 20% x (5% SVR) + 10% x (5% SVR) = 45%