Shortening overall treatment to 12 weeks of simeprevir plus PR in treatment-naïve chronic hepatitis C genotype 1 patients: assessment of baseline and Week 2 on-treatment predictors of SVR

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Disclosures

- Tarik Asselah is a speaker and investigator for AbbVie, BMS, Janssen, Gilead, Roche and MSD
Simeprevir (SMV)

- Once-daily capsule, HCV NS3/4A protease with pan-genotypic activity with the exception of genotype 3\(^1,2\)
- Approved in the EU, Japan, Canada, Russia, USA and in other regions
  - Approved in the EU and USA in combination with PegIFN or SOF for HCV genotype 1 and genotype 4\(^3\)
- Ongoing clinical development in IFN-free combinations in genotypes 1 and 4\(^4\)
- Good safety and tolerability profile in clinical trials\(^5–8\) and in real-world evidence studies\(^9–10\)

Background: treatment duration for SMV + PR in HCV genotype 1 treatment-naïve patients

* Determined by RGT: HCV RNA <25 IU/mL detectable or undetectable at Week 4 and undetectable at Week 12; RGT: response-guided therapy; RVR (HCV RNA undetectable at Week 4)

Background: treatment duration for SMV + PR in HCV genotype 1 treatment-naïve patients

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Background: 12 weeks triple therapy with protease inhibitor in HCV genotype 1 patients

- CONCISE study (TVR + PR):
  - Treatment-naïve and prior relapsers with HCV genotype 1 and *IL28B* CC
  - 12 weeks of therapy, if RVR (week 4) achieved
  - SVR rate of 87%

* Determined by RGT: HCV RNA <25 IU/mL detectable or undetectable at Week 4 and undetectable at Week 12; RGT: response-guided therapy
RVR (HCV RNA undetectable at Week 4)

1. Nelson et al. EASL 2013. Poster presentation
Background: 12 weeks triple therapy with protease inhibitor in HCV genotype 1 patients

- CONCISE study (TVR + PR)\(^1\):
  - Treatment-naïve and prior relapsers with HCV genotype 1 and \(IL28B\) CC
  - 12 weeks of therapy, if RVR (week 4) achieved
  - SVR rate of 87%

In the current study, we investigated the possibility of shortening SMV + PR treatment to 12 weeks using an algorithm based on on-treatment response at **Week 2**, irrespective of baseline characteristics

* Determined by RGT: HCV RNA <25 IU/mL detectable or undetectable at Week 4 and undetectable at Week 12; RGT: response-guided therapy; RVR (HCV RNA undetectable at Week 4)

1. Nelson et al. EASL 2013. Poster presentation
Study design (HPC3014; NCT 01846832)

- Patients meeting modified RGT criteria to stop all therapy after 12 weeks‡
- Patients not meeting modified RGT criteria will continue PR until Week 24
- Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4

*Patients in France had the option to extend treatment to 48 weeks – this option was taken by one patient
Roche COBAS® Taqman® LLOQ:25 IU/mL, LOD: 15 IU/mL. Protocol amendment for genotype 4 patients: in those with IL28B CT or TT, HCV RNA <25 IU/mL (undetectable) at Week 2 was required to qualify for the 12-week treatment arm
Study objectives and population

Primary objective
- Evaluate the efficacy, tolerability, and safety of 12 weeks of treatment with SMV + PR in patients meeting modified RGT criteria

Population
- Treatment naïve adults with HCV genotype 1 or 4 monoinfection with mild to moderate fibrosis
  - METAVIR stage F0–F2 (biopsy or non-invasive methods)
  - All IL28B genotypes
- This presentation will show data from the GT1 cohort

Shortening overall treatment to 12 weeks of SMV + PR according to early virologic response in treatment-naïve patients with chronic HCV genotype 4 infection and mild-to-moderate fibrosis
Presented 12 March: 17:48–17:55
Treatment algorithm for genotype 1

<table>
<thead>
<tr>
<th><em>IL28B</em> genotype</th>
<th>HCV RNA at <strong>Week 2 of treatment</strong></th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>&lt; 25 IU/mL undetectable</td>
<td>12 weeks*</td>
</tr>
<tr>
<td></td>
<td>&lt; 25 IU/mL detectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 25 IU/mL detectable</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

*To qualify for 12 weeks patients must also be <25 IU/mL undetectable at Week 4 and Week 8

Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4
Roche COBAS® Taqman® LLOQ:25 IU/mL, LOD: 15 IU/mL
Patient disposition

Screened (N=182)

Received study treatment, ITT (n=163)

Eligible for 12 weeks “12-week group” (n=123; 76%)

- Completed (n=123*)
- Ongoing (n=0)
- D/C SMV (n=0)

Not eligible for 12 weeks‡ “24-week group” (n=40)

- Completed (n=26)
- Ongoing (n=1)
- D/C SMV (n=13)

Treatment status

*One patient stopped both SMV and RBV (non-compliant) after RGT was determined (stopped at Week 11). The patient completed PegIFN;
‡Any patient who discontinued early and where eligibility could not be determined (n=2) was automatically included in the 24-week group
ITT: intent-to-treat; RGT: response-guided therapy
### Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>12-week group (n=123)</th>
<th>24-week group (n=40)</th>
<th>Overall (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>65 (53)</td>
<td>28 (70)</td>
<td>93 (57)</td>
</tr>
<tr>
<td>Age (years), median</td>
<td>47.0</td>
<td>49.5</td>
<td>47.0</td>
</tr>
<tr>
<td>BMI (kg/m²), median</td>
<td>25.0</td>
<td>25.45</td>
<td>25.10</td>
</tr>
<tr>
<td>Race, White, n/N (%)</td>
<td>98/107 (92)</td>
<td>32/33 (97)</td>
<td>130/140 (93)</td>
</tr>
<tr>
<td>IL28B genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>32 (26)</td>
<td>8 (20)</td>
<td>40 (25)</td>
</tr>
<tr>
<td>CT</td>
<td>73 (59)</td>
<td>20 (50)</td>
<td>93 (57)</td>
</tr>
<tr>
<td>TT</td>
<td>18 (15)</td>
<td>12 (30)</td>
<td>30 (18)</td>
</tr>
<tr>
<td>HCV RNA (log_{10} IU/mL), median</td>
<td>6.26</td>
<td>6.62</td>
<td>6.35</td>
</tr>
<tr>
<td>≤800 000 IU/mL, n (%)</td>
<td>33 (27)</td>
<td>3 (8)</td>
<td>36 (22)</td>
</tr>
<tr>
<td>HCV genotype subtype*, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>74 (60)</td>
<td>22 (55)</td>
<td>96 (59)</td>
</tr>
<tr>
<td>METAVIR score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0–F1</td>
<td>93 (76)</td>
<td>25 (63)</td>
<td>118 (73)</td>
</tr>
<tr>
<td>F2</td>
<td>29 (24)</td>
<td>15 (38)</td>
<td>44 (27)</td>
</tr>
</tbody>
</table>

*HCV geno/subtype is based on the NS5B assay, and if not available on the LIPA HCV II or Trugene results
On-treatment response, SVR4 and SVR12 in the 12-week group

**Virologic response (%):**
- < 25 IU/mL undetectable
- < 25 IU/mL detectable
- ≥25 IU/mL
- Missing

**Timepoint (weeks):**
- Week 2
  - <1 1/123
- Week 4
  - 100 123/123
- EOT
  - 100 123/123

Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system.
On-treatment response, SVR4 and SVR12 in the 12-week group

<table>
<thead>
<tr>
<th>Timepoint (weeks)</th>
<th>&lt; 25 IU/mL undetectable</th>
<th>&lt; 25 IU/mL detectable</th>
<th>≥25 IU/mL</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>71/123</td>
<td>1/123</td>
<td>58</td>
<td>1/123</td>
</tr>
<tr>
<td>Week 4</td>
<td>123/123</td>
<td>100</td>
<td>100</td>
<td>0/123</td>
</tr>
<tr>
<td>EOT</td>
<td>123/123</td>
<td>100</td>
<td>100</td>
<td>0/123</td>
</tr>
</tbody>
</table>

Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system.
On-treatment response, SVR4 and SVR12 in the 12-week group

Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system
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Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system
On-treatment response, SVR4 and SVR12 in the 12-week group

- **Week 2**
  - <25 IU/mL undetectable: 51/123
  - <25 IU/mL detectable: 71/123
  - ≥25 IU/mL: 1/123

- **Week 4**
  - <25 IU/mL undetectable: 123/123
  - <25 IU/mL detectable: 123/123
  - ≥25 IU/mL: 0

- **EOT**
  - <25 IU/mL undetectable: 123/123
  - <25 IU/mL detectable: 123/123
  - ≥25 IU/mL: 0

- **SVR4**
  - <25 IU/mL undetectable: 109/123
  - <25 IU/mL detectable: 11/123
  - ≥25 IU/mL: 0

- **SVR12**
  - <25 IU/mL undetectable: 81/123
  - <25 IU/mL detectable: 32/123
  - ≥25 IU/mL: 42/123

Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system.
On-treatment response, SVR4 and SVR12 in the 12-week group

Plasma HCV RNA determined by Roche COBAS® Taqman® HCV Test v2.0 assay for use with the high pure system
SVR12 by subgroups in the 12-week group

<table>
<thead>
<tr>
<th>Genotype subtype</th>
<th>IL28B genotype</th>
<th>METAVIR score</th>
<th>Baseline HCV RNA</th>
<th>Week 2 virologic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1a/other</td>
<td>31/49</td>
<td>69/93</td>
<td>27/33</td>
<td>39/51</td>
</tr>
<tr>
<td>G1b</td>
<td>50/74</td>
<td>40/73</td>
<td>54/90</td>
<td>41/71</td>
</tr>
<tr>
<td>CC</td>
<td>30/32</td>
<td>11/18</td>
<td>11/29</td>
<td>60</td>
</tr>
<tr>
<td>CT</td>
<td>55</td>
<td>77</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>TT</td>
<td>61</td>
<td>38</td>
<td>&lt;25 IU/mL undetect.</td>
<td></td>
</tr>
<tr>
<td>F0–F1</td>
<td></td>
<td></td>
<td>&lt;25 IU/mL detect.</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Predictors of response

- Analysis on baseline demographic and disease parameters associated with response is ongoing.

- Results of a multivariate analysis show *IL28B* CC genotype, F0/F1, and low HCV RNA to be predictors of response.

- Final analysis will be presented at an upcoming conference.
Any patient who discontinued early and where eligibility could not be determined was automatically included in the 24-week group.

*Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4
‡Two patients withdrew due to AEs (dyspnoea and fever)
## Safety: AEs by treatment group (entire treatment phase)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>12-week group (n=123)</th>
<th>24-week group* (n=40)</th>
<th>Overall (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>117 (95)</td>
<td>37 (93)</td>
<td>154 (95)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>4 (3)</td>
<td>1 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>AE leading to permanent stop*</td>
<td>-</td>
<td>4 (10)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>For all study drugs</td>
<td>-</td>
<td>3 (8)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>For PR only</td>
<td>-</td>
<td>1 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Worst grade 3 or 4 AE</td>
<td>29 (24)</td>
<td>8 (20)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Worst grade 3</td>
<td>23 (19)</td>
<td>3 (8)</td>
<td>26 (16)</td>
</tr>
<tr>
<td>Worst grade 4</td>
<td>3 (2)</td>
<td>3 (8)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>At least possibly related to SMV</td>
<td>6 (5)</td>
<td>2 (5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>110 (89)</td>
<td>36 (90)</td>
<td>146 (90)</td>
</tr>
<tr>
<td>At least possibly related to SMV</td>
<td>68 (55)</td>
<td>20 (50)</td>
<td>88 (54)</td>
</tr>
</tbody>
</table>

- SAEs experienced were pericoronitis, testicular necrosis, furuncle, alcohol withdrawal syndrome and rash (rash was the only AE considered possibly related to SMV)
- No grade 4 AEs were considered related to SMV; no discontinuations due to grade 3 AEs possibly related to SMV

*Results in the 24-week group are preliminary; ‡AEs leading to discontinuation in the four patients were dyspnoea (n=1), pyrexia (n=1) urinary incontinence (n=1); and rash (n=1). Rash and urinary incontinence were considered possibly related to SMV
Conclusions

- SMV + PR for 12 weeks resulted in a SVR12 rate of 66%
  - This was below the targeted 80%
- SVR rates after 12 weeks SMV + PR was not only dependent on early on-treatment response; baseline factors influenced SVR rates
  - Factors include IL28B genotype, fibrosis stage, baseline viral load
- Overall relapse rate in the 12-week group was 33%
  - This seemed to be driven by relapse rates in IL28B CT and TT patients with <25 detectable at Week 2
    - Therefore, the protocol was amended for ongoing genotype 4 patients
- Ongoing analysis to predict SVR rates based on positive predictors of response identified in multivariate analysis
- Safety was comparable to other SMV + PR trials with a similar AE profile to PR alone

1. Asselah et al. EASL 2015. Poster presentation P0792
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- **Robert Ryan, Oliver Lenz, Gino Van Dooren, Isabelle Lonjon-Domanec and Michael Schlag** are employees of Janssen Pharmaceuticals and may be Johnson and Johnson stockholders.
## Investigator sites

### Austria
- Linz, Austria
- Wien, Austria

### Belgium
- Brussels, Belgium
- Edegem, Belgium

### France
- Clichy, France
- Limoges Cedex 1, France
- Oeleans, France
- St Laurent Du Var, France

### Germany
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- Düsseldorf, Germany
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- Hamburg, Germany
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- Valencia, Spain
- Valme, Spain

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