Dr Janice Main
Imperial College Healthcare NHS Trust, London
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<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr Janice Main</td>
<td>None</td>
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</tbody>
</table>

**COMPETING INTEREST OF FINANCIAL VALUE £1,000:**

| Date     | October 2014 |
HEPATITIS C TREATMENT: FROM BENCH TO BEDSIDE
TREATMENT

Interferon, peginterferon, ribavirin +/- telaprevir/boceprevir

Side effects
Interactions
Disappointing results in HIV coinfection
TREATMENT

NOW
Oral only therapies
Directly acting antivirals (DAA)
Recognition of host and viral factors

Early access programme

Global/WHO issues
PSI-7977: ELECTRON
Interferon is not required for Sustained Virologic Response in Treatment-Naïve Patients with HCV GT2 or GT3

EJ Gane, CA Stedman, RH Hyland, RD Sorensen, WT Symonds, RG Hindes, MM Berrey

New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; Gastroenterology Department, Christchurch Hospital, Christchurch, New Zealand; Pharmasset, Inc., Princeton, NJ, United States.
<table>
<thead>
<tr>
<th>Time Wk</th>
<th>PSI-7977 RBV 12 weeks PEG</th>
<th>PSI-7977 RBV 8 weeks PEG</th>
<th>PSI-7977 RBV 4 weeks PEG</th>
<th>PSI-7977 RBV NO PEG</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%&lt;LOD</td>
<td>n</td>
<td>%&lt;LOD</td>
</tr>
<tr>
<td>2</td>
<td>9/11</td>
<td>82</td>
<td>7/8</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>11/11</td>
<td>100</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>11/11</td>
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</tr>
<tr>
<td>12</td>
<td>11/11</td>
<td>100</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>SVR4</td>
<td>11/11</td>
<td>100</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>SVR8</td>
<td>11/11</td>
<td>100</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>SVR12</td>
<td>11/11</td>
<td>100</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td>SVR24</td>
<td>6/6</td>
<td>100</td>
<td>5/5</td>
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## SOFOSBUVIR

**genotype 2 and 3**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>sofosbuvir 12 weeks n =10</th>
<th>Sofosbuvir ribavirin 8 weeks Plus PEG 8 weeks n =10</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR n (%)</td>
<td>6 (60%)</td>
<td>9/9 (100%)</td>
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</table>
# SOFOSBUVIR

**genotype 1**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>prev NR</th>
<th>reatment naïve</th>
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</thead>
<tbody>
<tr>
<td>sofosbuvir ribavirin 12 weeks</td>
<td>n = 10</td>
<td>Sofosbuvir ribavirin 12 weeks</td>
</tr>
<tr>
<td>SVR n (%)</td>
<td>1 (10%)</td>
<td>21 (84%)</td>
</tr>
</tbody>
</table>
PHARMA ISSUES

COSTS
Pharmasett (82 employees, net loss $91.2 million)
taken over by Gilead ($11 billion)

Sofosbuvir $1000/day
“SOVALDI – SO EXPENSIVE”

Products from different companies........
NEW TRIAL DESIGNS

SVR12
Interferon free
Shorter treatment courses
Response guided therapy (RGT)
HEPATITIS C

5'UTR

C E1 E2 NS2 NS3 NS4 NS5A NS5B

3'UTR

NS3/4 serine protease, RNA helicase
NS5A RNA dependent RNA polymerase
NS5B RNA dependent RNA polymerase

5'UTR antisense oligos
3'UTR ribozymes
HEPATITIS C – PI’s

5’UT

C  E1  E2  NS2  NS3  NS4  NS5A  NS5B  3’UT

NS3/4 serine protease

telaprevir
boceprevir
simeprevir
asunaprevir
ABT-450/r
MK5172
vaniprevir
faldaprevir
deleoprevir
HEPATITIS C – PI’s

Genotype 1
Low barrier to resistance
Interactions ++

NS3/4 serine protease
HEPATITIS C – NS5A inhibitors

5’UT

C E1 E2 NS2 NS3 NS4 NS5A NS5B

3’UT

NS5A RNA dependent RNA polymerase

ledipasvir
daclatasvir
ombitasvir (ABT- 267)
MK8742
HEPATITIS C – NS5A inhibitors

Pangenotypic
Low barrier to resistance

NS5A RNA dependent RNA polymerase
HEPATITIS C – NS5B inhibitors
NA’s

5’UT          3’UT

C  E1  E2  NS2  NS3  NS4  NS5A  NS5B

NS5B RNA dependent RNA polymerase

sofosbuvir
HEPATITIS C – NS5B inhibitors

NA’s

NS5B RNA dependent RNA polymerase

Pangenotypic
High barrier to resistance
HEPATITIS C-NS5B inhibitors
NNA’s

dasabuvir (ABT-333)
BMS- 791325
ABT-072
deleobuvir
HEPATITIS C-NS5B inhibitors
NNA’s

Genotype 1
Low barrier to resistance

NS5B RNA dependent RNA polymerase

5'UT 3'UT
Original Article

ABT-450/r–Ombitasvir and Dasabuvir with or without Ribavirin for HCV

Ferenci P et al, NEnglJMed, 2014
Study Designs.

HCV Genotype 1a

- **N=100**
  - ABT-450/r-ombitasvir + dasabuvir + ribavirin
  - Post-treatment period

- **N=205**
  - ABT-450/r-ombitasvir + dasabuvir + placebo
  - Post-treatment period

Day 0 | Wk 12 | Wk 24 | Wk 60
--- | --- | --- | ---

(assessment for sustained virologic response)

HCV Genotype 1b

- **N=210**
  - ABT-450/r-ombitasvir + dasabuvir + ribavirin
  - Post-treatment period

- **N=209**
  - ABT-450/r-ombitasvir + dasabuvir + placebo
  - Post-treatment period

Day 0 | Wk 12 | Wk 24 | Wk 60
--- | --- | --- | ---

(assessment for sustained virologic response)
Sustained Virologic Response at 12 Weeks after the End of Treatment.

HIV/HCV COINFECTION

Interferon based
Immunomodulatory > antiviral

PI’s/IFN/RBV

DAA’s +/- RBV +/- IFN

Drug interactions.....
ERADICATE: SOF/LDV in ARV-Treated and Untreated HCV/HIV-Coinfected Patients

- Single-arm phase II trial
- ARV use in 37 ARV-treated patients: efavirenz (41%), raltegravir (27%), rilpivirine (21%), rilpivirine and raltegravir (8%), efavirenz and raltegravir (3%)
- Median baseline CD4+ count: ARV treated 576 cells/mm$^3$ (range: 113-1612), ARV untreated 687 cells/mm$^3$ (range: 319-1287)
- SVR12 in ARV-treated patients: 100%; not yet available in ARV-untreated patients
- No clinically significant changes in HIV-1 RNA or CD4+ cell count
- SOF/LDV well tolerated, no discontinuations or grade 4 AEs


Sofosbuvir/ledipasvir 400/90 mg FDC tablet once daily.
C-WORTHY (genotype 1)

- MK-5172 (PI)
- MK-8742 (NS5A)
- +/- RBV

HIV pos n= 59

Sulkowski et al, EASL 2014
C-WORTHY (genotype 1)

- SVR4
- 90% no RBV
- 97% with RBV
Simeprevir (TMC435) with Peginterferon/Ribavirin in Patients Coinfected with HCV Genotype-1 and HIV-1: A Phase III Study

Dieterich D et al, Clin Infect Dis 2014
n = 106, RGT
Triple therapy 12 weeks
Treatment naïve (non-cirrhotic), prior relapsers – RGT PR 24 or 48 weeks
Prior nullresponders, prior partial responders, cirrhosis – PR 48 weeks

SVR12
79.2% in treatment naïve
57.1% in prior null responders
86.7% in prior relapsers
70.0% in prior partial responders
QUEST: No Benefit of Simeprevir if Q80K Positive

Q80K present in 34% of GT1a patients. No benefit of simeprevir if Q80K positive

Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV (PHOTON-1)

Sulkowski et al, JAMA 2014

Open-label, non-randomised, uncontrolled phase 3

**Treatment naïve**
Genotype 2 or 3 (n = 68)
SOF/RBV 12 weeks
Genotype 1 (n = 114)
SOF/RBV 24 weeks

**Treatment experienced**
Genotype 2 or 3 (n=41)
SOF/RBV 24 weeks
**Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV (PHOTON-1)**

Sulkowski et al, JAMA 2014

Open-label, non-randomised, uncontrolled phase 3

<table>
<thead>
<tr>
<th>Treatment naïve</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>76%</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Genotype 3</strong></td>
<td><strong>67%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment experienced</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td>92%</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>94%</td>
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</table>
IFN3 (IL28) and IFN4 and sofosbuvir

Impact on 2\textsuperscript{nd} phase of viral decay
N=60 with 24/52 SOF/RBV, no significant effect on SVR

Meissner JID (2014)
EARLY ACCESS PROGRAMME

Background
Some odd “results”
LIVER TRANSPLANTATION AND HCV

- graft reinfection
- immunosuppression
- interferon
- ribavirin
- combination
- PRE
- PERI
- POST
AASLD guidelines

GENOTYPE 1
TREATMENT NAÏVE
Eligible to receive IFN
PEG/RBV/SOF 12 weeks
Not eligible to receive IFN
SOF/SIM +/- RBV 12 weeks
AASLD guidelines

GENOTYPE 2
TREATMENT NAÏVE
RBV/SOF 12 weeks

GENOTYPE 3
TREATMENT NAÏVE
RBV/SOF 24 weeks
AASLD guidelines

GENOTYPE 4, 5, 6
TREATMENT NAÏVE
PEG/RBV/SOF 12 weeks
SUMMARY

Exciting new drugs/combinations
Shorter treatment courses
More effective (HIV pos = HIV neg)
Less toxic
Rapidly changing guidelines
Host and viral factors
Early access programme
Expensive
Can we eradicate HCV?