Daclatasvir and asunaprevir for hepatitis C infection

SUMMARY

Daclatasvir and asunaprevir are intended for use in the treatment of patients with chronic hepatitis C virus (HCV) infections genotype 1 and 4. If licensed daclatasvir and asunaprevir will offer an additional treatment option for patients with HCV genotypes 1 and 4, including those who have failed first line treatment with peginterferon (PEG-IFNα) and ribavirin (RBV). Daclatasvir is a small molecule HCV non-structural 5A (NS5A) replication complex inhibitor and asunaprevir is an oral selective inhibitor of the HCV NS3 protease.

The true incidence of HCV infection is difficult to establish, however recent estimates suggest that there are around 216,000 individuals chronically infected with HCV in the UK, with around 90% being genotype 1 and genotype 3. In 2011, there were 187 deaths registered in England and Wales1. The virus is acquired primarily through percutaneous exposure to contaminated blood. Most acute infections with HCV are asymptomatic with only 20% experiencing an overt hepatitis. Approximately 80% of people who are infected go on to develop chronic HCV which may result in inflammatory liver disease with the progressive development of hepatic fibrosis and cirrhosis. Chronic HCV is categorised as mild, moderate or severe depending on the extent of liver damage. The progression from infection to cirrhosis is variable in time but on average takes 40 years. About 30% of those who are infected with HCV develop cirrhosis within 20–30 years.

The choice of therapy for HCV is influenced by genotype. Patients with genotype 1 are treated with dual and triple combination therapy for a duration influenced by pre-treatment factors (including cirrhosis) or response to therapy. Patients with genotype 2 or 3 are usually treated with 24 weeks of PEG-IFNα-2 and RBV, whilst genotype 4 patients are treated with 48 weeks of PEG-IFNα-2 and RBV. All patients with chronic HCV (irrespective of the stage of the disease) are considered for therapy, with the aim of preventing the development of compensated and decompensated liver disease, and hepatocellular carcinoma. Daclatasvir and asunaprevir are currently in a number of trials comparing their effects on sustained viral response against placebo PEG-IFNα-2 and RBV alone.
**TARGET GROUP**

- Daclatasvir and asunaprevir for patients with hepatitis C virus (HCV) genotype 1b, who are treatment naïve or are ineligible, intolerant or have failed previous therapy with peginterferon (PEG-IFNα) and ribavirin (RBV).
- Daclatasvir and asunaprevir in combination with PEG-IFNα and RBV, for patients with HCV genotype 1 or 4 who have failed previous therapy with PEG-IFNα and RBV.
- Daclatasvir in combination with PEG-IFNα and RBV, for patients with HCV genotype 4 who are treatment naïve.
- Daclatasvir in combination with PEG-IFNα and RBV, for patients with HCV genotype 1b who are treatment naïve.

**TECHNOLOGY**

**DESCRIPTION**

Daclatasvir (BMS-790052) is a small molecule HCV non-structural 5A (NS5A) replication complex inhibitor. It has been shown to block two distinct stages of the viral lifecycle, namely viral RNA synthesis and virion assembly/secretion. Asunaprevir (BMS-650032) is an oral selective inhibitor of the HCV NS3 protease. In the phase III trials, daclatasvir was administered at 60mg once daily and asunaprevir at 100mg, 200mg or 400mg twice daily, both for 24 weeks.

**INNOVATION and/or ADVANTAGES**

If licensed daclatasvir and asunaprevir will offer an additional treatment option for patients with HCV genotypes 1 and 4, including those who have failed first line treatment with PEG-IFNα and RBV.

**DEVELOPER**

Bristol-Myers Squibb.

**AVAILABILITY, LAUNCH OR MARKETING**

In phase III clinical trials.

**PATIENT GROUP**

**BACKGROUND**

HCV is a member of the flaviviridae family of spherical, enveloped, positive-strand RNA viruses. There are six different HCV genotypes; genotype 2 and 3 are the most common in the UK and responsible for 50% of cases, closely followed by genotype 1 which is responsible for 45% of cases, and the most resistant to treatment. The virus is acquired primarily through percutaneous exposure to contaminated blood. Most acute infections with HCV are asymptomatic with only 20% experiencing an overt hepatitis. Approximately 80% of people who are infected go on to develop chronic HCV which may result in inflammatory liver disease with the progressive development of hepatic fibrosis and cirrhosis. Chronic HCV is categorised as mild, moderate or severe depending on the extent of liver damage.
The progression from infection to cirrhosis is variable in time but on average takes 40 years\textsuperscript{4}. About 30\% of those who are infected with HCV develop cirrhosis within 20–30 years\textsuperscript{8,9}. Patients with detectable levels of HCV DNA have an increased risk of hepatic and extrahepatic disease\textsuperscript{10}. There are also a number of other factors known to increase the rate of progression such as age, male sex, excessive alcohol consumption and HIV co-infection\textsuperscript{5}.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The true incidence of HCV infection is difficult to establish, however recent estimates suggest that there are around 216,000 individuals chronically infected with HCV in the UK\textsuperscript{11}, with around 90\% infected with HCV genotype 1 or genotype 3\textsuperscript{12}. Chronic HCV was the primary cause of 2,404 admissions to hospitals in England in 2011-12 resulting in 3,332 bed days\textsuperscript{12} (ICD-10 B17.1, B18.2). In 2011, there were 187 deaths registered in England and Wales\textsuperscript{13}. HCV is the major cause of liver transplantation in Europe\textsuperscript{14}; in 2011 there were 102 first registrations for liver transplant as a result of post-HCV cirrhosis in England\textsuperscript{8}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- NICE technology appraisal in development. Hepatitis C (children and young people) – peginterferon alfa and ribavirin. Expected August 2013\textsuperscript{15}.
- NICE technology appraisal. Telaprevir for the treatment of genotype 1 chronic hepatitis C. (TA252). April 2012\textsuperscript{17}.
- NICE technology appraisal. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. (TA75). 2004\textsuperscript{19}.

**Other Guidance**
- European Association for the Study of the LIVER (EASL) Clinical Practice Guidelines: Management of hepatitis C virus infection. 2011\textsuperscript{20}.
- Department of Health. Hepatitis C: quick reference guide for primary care. 2009\textsuperscript{21}.
- Royal College of General Practitioners. Guidance for the prevention, testing, treatment and management of hepatitis C in primary care. 2007\textsuperscript{22}.
- SIGN. Management of hepatitis C. 2013\textsuperscript{23}.
- British Association of Sexual Health and HIV. United Kingdom national guideline on the management of the viral hepatitides A, B & C. 2005\textsuperscript{24}.
**EXISTING COMPARATORS and TREATMENTS**

The choice of therapy for HCV is influenced by genotype. Patients with genotype 1 are treated with dual and triple combination therapy for a duration influenced by pre-treatment factors (including cirrhosis) or response to therapy. Patients with genotype 2 or 3 are usually treated with 24 weeks of PEG-IFNα-2 and RBV, whilst genotype 4 patients are treated with 48 weeks PEG-IFNα-2 and RBV. All patients with chronic HCV (irrespective of the stage of the disease) are considered for therapy\(^5\), with the aim of preventing the development of compensated and decompensated liver disease, and hepatocellular carcinoma.

Current treatment options include\(^5,19\):
- A combination of RBV and PEG-IFNα-2a (Pegasys, Roche) or PEG-IFNα-2b (ViraferonPeg, Schering-Plough).
- Telaprevir in combination with PEG-IFNα and RBV.
- Boceprevir in combination with PEG-IFNα and RBV.

Successful treatment is usually indicated by a sustained viral response (SVR), which is defined as undetectable serum HCV RNA 6 months after the end of treatment\(^4\). The proportion of people with HCV genotype 1 who show an SVR finishing a course of treatment with PEG-IFNα/RBV is about 40% to 50%\(^4,10\) and 60% to 80% in patients treated with triple therapy boceprevir/telaprevir and PEG-IFNα/RBV\(^a\). This compares to approximately 75% to 85% of people with HCV genotype 2 or 3, and 50% to 75% for other genotypes (4, 5, and 6) treated with dual therapy PEG-IFNα/RBV\(^4,10\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>COMMAND-3, NCT01492426, AI444-052, 2011-004237-14; daclatasvir with PEG-IFNα-2a and RBV vs telaprevir with PEG-IFNα-2a and RBV; phase III.</th>
<th>NCT01389323, AI444-038; daclatasvir with PEG-IFNα-2a and RBV; phase III.</th>
<th>NCT01448044, AI444-042, 2011-002793-23; daclatasvir with PEG-IFNα-2a and RBV vs placebo with PEG-IFNα-2a and RBV; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry(^26).</td>
<td>Trial registry(^27).</td>
<td>Trial registry(^28).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>USA and Puerto Rico.</td>
<td>EU (incl UK), USA and Puerto Rico.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=600 (planned); aged ≥18 years; chronically infected with HCV genotype 1a or 1b; treatment naive.</td>
<td>n=230 (planned); aged ≥18 years; chronically infected with HCV genotype 1a or 1b; treatment naive.</td>
<td>n=120 (planned); aged ≥18 years; chronically infected with HCV genotype 4; treatment naive.</td>
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</table>

\(^a\) Expert personal communication.
| Schedule | Randomised to oral daclatasvir 60mg once daily for 24 weeks in combination with subcutaneous (SC) PEG-IFNα-2a 180µg weekly and oral RBV 1,000mg or 1,200mg per day, both for 24 or 48 weeks; or oral telaprevir 750mg three times daily for 12 weeks, in combination with SC PEG-IFNα-2a 180µg weekly and oral RBV 1,000mg or 1,200mg per day, both for 24 or 48 weeks. | Oral daclatasvir 60mg once daily for 24 weeks in combination with SC PEG-IFNα-2a 180µg weekly and oral RBV 1,200mg per day, both for 24 or 48 weeks. | Randomised to oral daclatasvir 60mg once daily for 24 weeks in combination with SC PEG-IFNα-2a 180µg weekly and oral RBV 1,000mg or 1,200mg daily (dependent on weight), both for 24 or 48 weeks; or placebo in combination with SC PEG-IFNα-2a 180µg weekly and oral RBV 1,000mg or 1,200mg daily (dependent on weight), both for 48 weeks. |
| Follow-up | Active treatment period 24 or 48 weeks. Follow-up 24 or 48 weeks thereafter. | Active treatment period 24 or 48 weeks. Follow-up 24 or 48 weeks thereafter. | Active treatment period 24 or 48 weeks. Follow-up 24 or 48 weeks thereafter. |
| Primary outcome/s | SVR12 b in genotype 1b patients. | SVR24. | SVR12. |
| Secondary outcome/s | Haemoglobin <10g/dL; rash events; SVR12; SVR4; HCV RNA undetectable at week 4 and 12; SVR24; SVR12 based on IL28B rs12979860 single nucleotide polymorphism (SNP). | Safety: SVR proportion of patients with CC, CT or TT genotype at the IL28B rs12979860 SNP who achieve SVR. | SVR; safety; SVR12 or SVR24 by IL28B rs12979860 SNP. |
| Expected reporting date | Estimated study completion date Mar 2014. | Estimated study completion date Apr 2014. | Estimated study completion date May 2014. |
| Trial | NCT01573351, AI447-029, 2011-005422-21; asunaprevir with daclatasvir, PEG-IFNα-2a and RBV; phase III. | NCT01581203, AI447-028, 2011-005446-35; asunaprevir with daclatasvir; phase III. | NCT01428063, AI444-026, 2011-000836-27; asunaprevir with daclatasvir, PEG-IFNα-2a and RBV; phase II. |
| Location | EU, USA, Canada and other countries. | EU (incl UK), USA, Canada and other countries. | EU (incl UK), USA, Canada and other countries. |
| Design | Uncontrolled, single arm. | Randomised, placebo-controlled for treatment naïve cohort only; non-randomised single arm for all other cohorts. | Non-randomised. |

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b SVR, defined as HCV RNA < limit of quantification (LOQ). SVR12 defines SVR after 12 weeks of therapy.
<p>| Participants | n=390 (planned); aged ≥18 years; HCV genotype 1 or 4; null or partial response to treatment with PEG-IFNα-2a and RBV. | n=725 (planned); aged ≥18 years; HCV genotype 1b; null or partial response to treatment with PEG-IFNα-2a and RBV, ineligible for treatment with PEG-IFNα-2a and RBV due to neutropenia, anaemia depression or thrombocytopenia with cirrhosis, or treatment naïve. | n=300 (planned); aged ≥18 years; prior participation in any BMS-790052, BMS-650032 or BMS-791325 trial and assigned to control arm (PEG-IFNα-2a/RBV and/or placebo); HCV genotype 1, 2, 3 or 4 (mixed genotypes not permitted). |
| Schedule | Oral asunaprevir 100mg twice daily in combination with oral daclatasvir 60mg once daily, SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg per day; all for 24 weeks. | Arm 1 Null or partial responders to PEG-IFNα-2a and RBV. Oral asunaprevir 100mg twice daily in combination with oral daclatasvir 60mg once daily. Arm 2 Intolerant or ineligible to receive PEG-IFNα-2a and RBV. Oral asunaprevir 100mg twice daily in combination with oral daclatasvir 60mg once daily, both for 24 weeks. Arm 3 PEG-IFNα-2a and RBV treatment naïve. Randomised to oral asunaprevir 100mg twice daily in combination with oral daclatasvir 60mg once daily, both for 24 weeks; or placebo for 12 weeks. | Arm 1 HCV genotypes 1 and 4, prior non-responders to PEG-IFNα-2a and RBV. Oral asunaprevir 100mg or 200mg twice daily in combination with oral daclatasvir 60mg once daily, SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. Arm 2 HCV genotypes 2 and 3, prior non-responders to PEG-IFNα-2a and RBV. Oral daclatasvir 60mg once daily in combination with SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. Arm 3 Treatment naïve genotype 1b. Oral asunaprevir 100mg twice daily in combination with oral daclatasvir 60mg once daily; all for 24 weeks. |
| Follow-up | Active treatment period 24 weeks. Follow-up 24 weeks thereafter. | Active treatment period 24 weeks. Follow-up 24 weeks thereafter. | Active treatment period 24 weeks. Follow-up 24 weeks thereafter. |
| Primary outcome/s | SVR12 in genotype 1 patients. | SVR12 in null or partial responders and treatment naïve groups. | SVR12 in genotype 1 prior non-responders to PEG-IFNα-2a and RBV. |</p>
<table>
<thead>
<tr>
<th>Secondary outcome/s</th>
<th>Safety; SVR; SVR12 by the rs12979860 SNP; SVR12 in genotype 4 patients.</th>
<th>SVR; SVR12 in intolerant or ineligible groups; safety; laboratory abnormalities; genotype 1b patients with SVR12 by the rs12979860 SNP.</th>
<th>SVR; SVR12 in genotype 2, 3 and 4 prior non-responders to PEG-IFNα-2a and RBV and treatment naïve genotype 1b patients; safety; drug-resistant variants associated with virologic failure for each HCV genotype and treatment regimen.</th>
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</table>

**Trial**

<table>
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<tr>
<th>NCT00874770, Al444-014, 2009-010149-29; daclatasvir with PEG-IFNα-2a and RBV vs placebo with PEG-IFNα-2a and RBV; phase II.</th>
<th>NCT01170962, Al444-011, 2010-019378-34; daclatasvir with PEG-IFNα-2a and RBV vs placebo with PEG-IFNα-2a and RBV; phase II.</th>
<th>NCT01012895, Al447-011, 2011-005446-35; asunaprevir and daclatasvir vs asunaprevir, daclatasvir and RBV vs daclatasvir, asunaprevir, RBV and PEG-IFNα-2a; phase II.</th>
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**Sponsor**

|-----------------------|-----------------------|-----------------------|

**Status**

|------------|---------------------------|---------|

**Source of information**

<table>
<thead>
<tr>
<th>Publication31</th>
<th>Trial registry32</th>
<th>Trial registry33</th>
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**Location**

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<th>USA and France.</th>
<th>EU, USA, Canada and other countries.</th>
<th>USA, France and Puerto Rico.</th>
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</table>

**Design**

|----------------------------------|----------------------------------|-----------------------------|

**Participants**

<table>
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<tr>
<th>n=48; 18 to 70 years; chronic HCV genotype 1 infection; treatment naïve.</th>
<th>n=421; 18 to 70 years; non or partial responders to prior PEG-IFNα-2a and RBV therapy.</th>
<th>n=120 (planned); 18 to 70 years; HCV genotype 1 null responders; arms 3 and 4 restricted to genotype 1b patients.</th>
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**Schedule**

| Randomised to: Arm 1 Oral daclatasvir 3mg daily in combination with SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 48 weeks. Arm 2 Oral daclatasvir 10mg daily in combination with SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 48 weeks. Arm 3 Oral daclatasvir 60mg daily in combination with SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 48 weeks. Arm 4 Placebo in combination with SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily; all for 48 weeks. | Randomised to: Arm 1 Prior non-responders. Oral daclatasvir 20mg daily in combination with SC PEG-IFNα-2a 180µg once weekly, and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. Arm 2 Prior non-responders. Oral daclatasvir 60mg daily in combination with SC PEG-IFNα-2a 180µg once weekly, and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. Arm 3 Prior partial responders. Oral daclatasvir 20mg daily in combination with SC PEG-IFNα-2a 180µg once weekly, and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. Arm 4 Prior partial responders Oral daclatasvir 20mg daily in combination with SC PEG-IFNα-2a 180µg once weekly, and oral RBV 1,000mg or 1,200mg daily; all for 24 weeks. | Randomised to: Arm 1 Oral daclatasvir 60mg daily in combination with oral asunaprevir 600mg twice daily for 24 weeks. Arm 2 Oral daclatasvir 60mg daily in combination with oral asunaprevir 600mg twice daily; SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily (depending on weight); all for 24 weeks. Arm 3 Oral daclatasvir 60mg daily in combination with oral asunaprevir 200mg twice daily for 24 weeks. Arm 4 Oral daclatasvir 60mg daily in combination with oral asunaprevir 200mg once daily for 24 weeks. Arm 5 Oral daclatasvir 60mg daily in combination with oral asunaprevir 200mg twice daily, SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or... |
**NIHR Horizon Scanning Centre**

<table>
<thead>
<tr>
<th>Arm 5</th>
<th>Arm 6</th>
<th>Arm 7</th>
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<tbody>
<tr>
<td>Prior partial responders</td>
<td>Oral daclatasvir 60mg daily in combination with oral asunaprevir 200mg once daily, SC PEG-IFNα-2a 180µg once weekly and oral RBV 1,000mg or 1,200mg daily (depending on weight); all for 24 weeks.</td>
<td>Oral daclatasvir 60mg daily in combination with oral asunaprevir 200mg twice daily and RBV 1,000mg or 1,200mg daily; all for 24 weeks.</td>
</tr>
<tr>
<td>Placebo in combination with SC PEG-IFNα-2a 180µg once weekly, and oral RBV 1,000mg or 1,200mg daily, all for 24 weeks.</td>
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**Follow-up**
- Active treatment period 48 weeks. Follow-up 24 weeks thereafter.
- Active treatment period 24 or 48 weeks. Follow-up 24 or 48 weeks thereafter.
- Active treatment period 24 weeks. Follow-up 48 weeks thereafter.

**Primary outcome/s**
- Safety; HCV RNA determined by extended rapid virologic response (eRVR).
- eRVR; SVR; safety.
- HCV RNA.

**Secondary outcome/s**
- RVR; early virologic response (EVR); complete early virological response (cEVR) SVR; resistant variants with clinical failure.
- RVR; cEVR; SVR12; genotypic substitutions associated with virologic failure.
- Safety; pharmacokinetics.

**Key results**
- For daclatasvir 3mg, 10mg 60mg and placebo respectively (80% CI):
  - eRVR, 42% (22-64%), 83% (61-96%), 75% (53-90%), 8% (1-29%); RVR, 42% (22-64%), 92% (71-99%), 83% (61-96%), 8% (1-29%); cEVR, 58% (36-78%), 83% (61-96%), 83% (61-96%), 42% (22-64%); SVR at 12 weeks, 42% (22-64%), 92% (71-99%), 83% (61-96%), 25% (10-48%); SVR at 24 weeks, 42% (22-64%), 83% (61-96%), 83% (61-96%) 25% (10-48%); virological failure, 58%, 17%, 17%, 75%.
  - eRVR daclatasvir 20mg group, 18.0% and 25.7% for prior null responders or prior partial respectively; eRVR daclatasvir 60mg group, 19.7% and 35.8% for prior null responders or prior partial responders respectively; SVR24 daclatasvir 20mg group, 18.8% and 24.3% for prior null responders and prior partial responders respectively; SVR24 daclatasvir 60mg group, 22.0% and 43.3% for prior null responders and prior partial responders respectively.

**Adverse effects (AEs)**
- AEs occurred with similar frequency across groups.

**Expected reporting date**
- Previously reported as December 2012.
- Estimated study completion date Feb 2014.
ESTIMATED COST and IMPACT

COST

The cost of daclatasvir and asunaprevir is not yet known. The costs of currently licensed treatments are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose*</th>
<th>24 week cost</th>
<th>48 week cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFNa-2a</td>
<td>180µg once weekly</td>
<td>£2,986</td>
<td>£5,971</td>
</tr>
<tr>
<td>PEG-IFNa-2b</td>
<td>120µg once weekly</td>
<td>£3,828</td>
<td>£7,656</td>
</tr>
<tr>
<td>RBV</td>
<td>1,200mg daily</td>
<td>£2,220</td>
<td>£4,440</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>2,250mg daily</td>
<td>£44,796</td>
<td>-</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>800mg daily</td>
<td>£16,800</td>
<td>-</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

Impact on Services
- Increased use of existing services
- Decreased use of existing services: oral treatment option.
- Re-organisation of existing services
- Need for new services
- None identified

Impact on Costs
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- None identified

Other Issues
- Clinical uncertainty or other research question
- None identified

REFERENCES

2 Guedj J, Dahari H, Rong L et al. Modelling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proceedings of the National Academy of Sciences 2013;110(10):3991-3996.

* Based on average weight 77.9kg.
7 National Institute for Health Research Horizon Scanning Centre. BI 201335 for chronic hepatitis C infection. Birmingham NIHR HSC; June 2012.

ClinicalTrials.gov. Study to determine the effectiveness of antiviral combination therapy to treat hepatitis C virus (HCV) infected patients who have previously failed standard of care http://clinicaltrials.gov/ct2/show/NCT01012895 Accessed 21 August 2013.