Horizon Scanning Centre
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Sofosbuvir for chronic hepatitis C infection with compensated liver disease

SUMMARY **NIHR HSC ID: 7614**

Sofosbuvir is a second generation uridine nucleoside analogue polymerase inhibitor of hepatitis C (HCV). Sofosbuvir is a chirally pure isomer of PSI 7851. The two isomers of PSI 7851, PSI 7976 and sofosbuvir, are converted *in vivo* to the same active triphosphate. Sofosbuvir is administered orally and in clinical trials has been administered once daily at 400mg for 8, 12 or 24 weeks in combination with ribavirin (RBV) and with or without peg-interferon (peg-IFN).

The true incidence of HCV infection is difficult to establish, however recent estimates suggest that there are 173,000 chronically infected HCV patients in England and Wales of whom 17,000 patients are currently receiving treatment. Chronic HCV was the primary cause of 2,967 admissions to hospitals in England in 2010-11 resulting in 2,688 bed days (ICD-10 B17.1, B18.2). In 2010, there were 166 deaths registered in England and Wales. HCV is the major cause of liver transplantation in Europe.

Patients with genotype 1 are treated with triple combination therapy for a duration influenced by pre-treatment factors or response to therapy. Current treatment options include combination of RBV and peginterferon alfa-2a or peginterferon alfa-2b, telaprevir in combination with peginterferon alfa and RBV or boceprevir in combination with peginterferon alfa and RBV. Patients with genotype 2 or 3 are usually treated with 24 weeks of peg-IFN and RBV.

Sofosbuvir is in phase III clinical trials comparing its effect on virological response against treatment with a number of alternative standard treatment options. The current phase III trials are expected to be complete by 2013.

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NHS
National Institute for Health Research

TARGET GROUP

- Hepatitis C (HCV) infection; genotypes 1, 2, 3, 4, 5 and 6; compensated liver disease, including cirrhosis.

TECHNOLOGY

DESCRIPTION

Sofosbuvir (GS-7977; PSI-7977) is a second generation uridine nucleoside analogue polymerase inhibitor of HCV. Sofosbuvir is a chirally pure isomer of PSI 7851. The two isomers of PSI 7851, PSI 7976 and sofosbuvir, are converted *in vivo* to the same active triphosphate. Sofosbuvir is administered orally and in clinical trials has been administered once daily at 400mg for 8, 12 or 24 weeks in combination with RBV and with or without peg-IFN.

INNOVATION and/or ADVANTAGES

If licensed, sofosbuvir may offer an additional treatment option for HCV that may allow treatment duration to be reduced to 12 weeks. In genotypes 2 and 3, sofosbuvir may also offer an oral treatment option for patients who are unwilling or unable to take peg-IFN.

DEVELOPER

Gilead Sciences.

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[1,2]. The virus is acquired primarily through percutaneous exposure to contaminated blood[3]. Most acute infections with HCV are asymptomatic with only 20% experiencing an overt hepatitis[3]. Approximately 80% of people who are infected go on to develop chronic HCV[2], which may result in inflammatory liver disease with the progressive development of hepatic fibrosis and cirrhosis[4]. 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[2]. About 30% of those who are infected with HCV develop cirrhosis within 20–30 years[5,6]. Patients with detectable levels of HCV DNA have an increased risk of hepatic and extraheptic disease[7]. 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[3].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- The Blood Borne Virus Action Plan for Wales 2009-2014. 2008.
- Hepatitis C Action Plan for England. 2004.

CLINICAL NEED and BURDEN OF DISEASE

The true incidence of HCV infection is difficult to establish, however recent estimates suggest that there are 173,000 chronically infected HCV patients in England and Wales[8], and around 91,900 are diagnosed in the UK (five out of six chronic HCV patients are unaware of their infection status[6]). 17,000 patients are currently receiving treatment and of these, 45% (7,650) are genotype 1[6]. It is estimated that there will be 7,922 genotype 1 chronic HCV patients being treated in 2016[6]. Chronic HCV was the primary cause of 2,967 admissions to hospitals in England in 2010-11 resulting in 2,688 bed days[9] (ICD-10 B17.1, B18.2). In 2010, there were 166 deaths registered in England and Wales[10]. HCV is the major cause of liver transplantation in Europe[11], in 2011 there were 102 first registrations for liver transplant as a result of post-HCV cirrhosis in England[6].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Hepatitis C (children and young people) – peginterferon alfa and ribavirin. Expected August 2013[12].
- NICE technology appraisal. Telaprevir for the treatment of genotype 1 chronic hepatitis C. (TA252). April 2012[13].
- NICE technology appraisal. Boceprevir for the treatment of genotype 1 chronic hepatitis C. (TA253). April 2012[14].
- NICE technology appraisal. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. (TA200). 2010[3].
- NICE technology appraisal. Peginterferon alfa and ribavirin for the treatment of mild hepatitis C. (TA106). 2006[15].
- NICE technology appraisal. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. (TA75). 2004[16].

Other Guidance

- Department of Health. Hepatitis C: quick reference guide for primary care. 2009[17].
- Royal College of General Practitioners. Guidance for the prevention, testing, treatment and management of hepatitis C in primary care. 2007[18].
- SIGN. Management of hepatitis C. 2006[19].
- British Association of Sexual Health and HIV. United Kingdom national guideline on the management of the viral hepatitides A, B & C. 2005[20].
- British Society of Gastroenterology. Guidance on the treatment of hepatitis C incorporating the use of pegylated interferon. 2003[21].

EXISTING COMPARATORS and TREATMENTS

The choice of therapy for HCV is influenced by genotype. Patients with genotype 1 are treated with 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-IFN and RBV. All patients with chronic HCV (irrespective of the stage of the disease) are considered for therapy[3], with the aim of preventing the development of compensated and decompensated liver disease, and hepatocellular carcinoma.

Current treatment options include[3]:

- A combination of RBV and peginterferon alfa-2a (Pegasys, Roche) or peginterferon alfa-2b (ViraferonPeg, Schering-Plough).
- Telaprevir in combination with peginterferon alfa and RBV (Incivo, Janssen-Cilag).
- Boceprevir in combination with peginterferon alfa and RBV (Victrelis, Merck Sharp & Dohme).

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[2]. The proportion of people with HCV genotype 1 who show a SVR finishing a course of treatment with pegIFN/RBV is about 40% to 50%, compared to approximately 75% to 85% of people with HCV genotype 2 or 3, and 50% to 75% for other genotypes (4, 5, and 6)[2,9].

EFFICACY and SAFETY

Trial	FISSON, NCT01497366; sofosbuvir with RBV vs peg-IFN with RBV; phase III.	POSITRON, NCT01542788; sofosbuvir with RBV vs placebo; phase III.
Sponsor	Gilead Sciences.	Gilead Sciences.
Status	Ongoing.	Ongoing.
Source of information	Trial registry[22].	Trial registry[23].
Location	EU, USA, Canada and other countries.	EU, USA, Canada and other countries.
Design	Randomised, active-controlled.	Randomised, placebo-controlled.
Participants	n=500 (planned); aged >18 years of age; HCV genotype 2 or 3; treatment naive.	n=240 (planned); aged >18 years of age; HCV genotype 2 or 3; intolerant, ineligible or unwilling to take peg- IFN.
Schedule	Randomised to sofosbuvir 400mg once daily in combination with RBV for 12 weeks or peg-IFN in combination with RBV for 24 weeks.	Randomised to sofosbuvir 400mg once daily in combination with RBV or sofosbuvir placebo with RBV placebo.
Follow-up	Active treatment period of 12 or 24 weeks, follow-up 24 weeks.	Active treatment period 12 weeks, follow-up 12 weeks.
Primary outcome/s	SVR at week 12.	SVR at week 12.
Secondary outcome/s	Safety, SVR at week 24, HCV RNA, alanine aminotransferase (ALT) normalisation, virologic failure, drug resistance.	Efficacy 4 and 24 weeks post dosing, HCV RNA during and post-treatment, viral resistance.
Expected reporting date	Estimated study completion Oct 2013.	Estimated study completion Jan 2013.

Trial	FUSION, NCT01604850; sofosbuvir with RBV 12 vs 16 weeks; phase III.	NEUTRINO, NCT01641640; sofosbuvir with peg-IFN and RBV; phase III.	NCT01667731;sofosbuvir 400mg with RBV; phase III
Sponsor	Gilead Sciences.	Gilead Sciences.	Gilead Sciences.
Status	Ongoing.	Ongoing.	Ongoing.
Source of information	Trial registry[24].	Trial registry[25] .	Trial registry[26].
Location	USA.	USA.	USA and Puerto Rico.
Design	Randomised.	Single arm.	Open label, single-arm.
Participants	n=200 (planned); aged >18 years of age; HCV genotype 2 or 3; treatment experienced.	n=300 (planned); aged >18 years of age; HCV genotype 1, 4, 5 or 6 treatment naive.	n=100 (planned); aged >18 years of age; genotype 2 or 3 HCV and HIV co infection; treatment-naive (including IFN-ineligible) and treatment experienced participants.
Schedule	Randomised to sofosbuvir 400mg once daily in combination with RBV for 12 weeks or 16 weeks.	Sofosbuvir 400mg once daily in combination with RBV and peg-IFN.	Sofosbuvir 400mg once daily in combination with RBV for 12- 24 weeks based on treatment experience.
Follow-up	Active treatment period of 12 or 16 weeks, follow-up 24 or 28 weeks.	Active treatment period 12 weeks, follow-up 24 weeks.	Active treatment period 12-24 weeks.
Primary outcome/s	SVR at week 12 and safety and tolerability at 12 and 16 weeks	SVR at week 12.	SVR at 12, safety and tolerability.
Secondary outcome/s	Safety, SVR at week 4 and 24, HCV RNA, ALT normalisation, virologic failure, drug resistance.	Efficacy 4 and 24 weeks post dosing, HCV RNA during and post-treatment, viral resistance.	SVR 4 and 24, RNA HCV kinetics, viral resistance.
Expected reporting date	Estimated study completion July 2013.	Estimated study completion July 2013.	Estimated study completion Mar 2013.

Trial	ATOMIC, NCT01329978; sofosbuvir with peg-IFN and RBV for 12 or 24 weeks; phase II.	QUANTUM, NCT014435044; sofosbuvir and PSI-352938[a], PSI-352938 monotherapy, sofosbuvir, PSI-352938 and RBV or sofosbuvir and RBV; phase II.	NCT01441180; sofosbuvir with or without RBV; phase II.
Sponsor	Gilead Sciences.	Gilead Sciences.	Gilead Sciences.
Status	Ongoing.	Ongoing.	Ongoing.
Source of information	Trial registry[27].	Trial registry[28], manufacturer[29].	Trial registry[30], manufacturer.
Location	USA and Puerto Rico.	USA and Puerto Rico.	USA.
Design	Randomised, open-label.	Randomised, placebo-controlled.	Randomised, open-label.
Participants	n=325 (planned); aged >18 years of age; HCV	n=239 (planned) aged >18 years of age; chronic	n=79 (planned) aged >18 years of age; HCV genotype

[a] Gilead Sciences was also developing PSI-352938, an orally-active NS5A protein inhibitor, for the treatment of HCV infections clinical trials have now been discontinued.

	genotype 1, 4, 5, 6 or indeterminate; treatment naive.	HCV infection; treatment naive.	1; treatment naive.
Schedule	Randomised to Arm 1: sofosbuvir 400mg with peg-IFN and RBV for 12 weeks Arm 2: sofosbuvir 400mg with peg-IFN and RBV for 24 weeks Arm 3: sofosbuvir 400mg with peg-IFN and RBV for 12 weeks. At week 12 participants re-randomised to sofosbuvir monotherapy or sofosbuvir with RBV.	Randomised to Arm 1: sofosbuvir 400mg with PSI-352938 300mg once daily for 12 weeks. Arm 2: PSI-352938 300mg once daily for 12 weeks. Arm 3: sofosbuvir with RBV 400mg once daily for 12 weeks. Arm 4: sofosbuvir 400mg with PSI-352938 300mg and RBV once daily for 12 weeks. Arm 5: PSI-352938 300mg once daily for 24 weeks. Arm 6: Sofosbuvir 400mg once daily with PSI-352938 300mg once daily for 24 weeks. Arm 7: sofosbuvir 400mg once daily with RBV for 24 weeks. Arm 8: sofosbuvir 400mg with PSI-352938 300mg and RBV once daily for 24 weeks. Arm 9: Placebo for 24 weeks followed by randomisation through arms 1-8.	Randomised to sofosbuvir 400mg once daily alone or in combination with RBV.
Follow-up	Active treatment period of 12 or 24 weeks, follow-up 12 weeks.	Active treatment period up to 24 weeks, follow-up 48 weeks post-treatment.	Active treatment period of 24 weeks, follow-up 72 weeks.
Primary outcome/s	Adverse effects (AEs), efficacy at 12 or 24 weeks.	Decreased HCV RNA at 24 weeks.	AEs.
Secondary outcome/s	HCV RNA, SVR at week 12 or 24.	AEs, HCV RNA, ALT normalisation, SVR at week 48, drug resistance,	None reported.
Key results	-	25 participants randomised to 12 week treatment arms. At 4 weeks post-treatment results available for 17 genotype 1 participants: 59% (n=10) remained HCV RNA undetectable and 41% (n=7) experienced viral relapse. 7 participants who have reached 8 weeks post treatment period have remained HCV RNA undetectable.	Interim results: 25 participants completed 12 weeks of treatment 88% (n=22) remained HCV RNA undetectable 4 weeks following completion. 3 experienced viral relapse.

Adverse effects (AEs)	-	Sofosbuvir was well tolerated, with no participants experiencing viral rebound and no discontinuation due to AEs.	Sofosbuvir was well tolerated, with no participants experiencing viral rebound and no discontinuation due to AEs. Most common AEs included fatigue, dizziness and headache. Two grade 3-4 lab abnormalities reported.
Expected reporting date	Estimated study completion Sep 2012.	Estimated study completion Apr 2013.	Estimated study completion Aug 2013.

Trial	ELETRON, NCT01260350; sofosbuvir with RBV, peg-IFN or GS-5885[b]; phase II.	NCT01188772; sofosbuvir vs placebo, both with peg-IFN and RBV; phase II.
Sponsor	Gilead Sciences.	Gilead Sciences.
Status	Ongoing.	Complete, but unpublished.
Source of information	Trial registry[31].	Trial registry[32], manufacturer.
Location	New Zealand.	USA and Puerto Rico.
Design	Randomised, active-controlled.	Randomised, placebo-controlled.
Participants	n=190 (planned); aged >18 years of age; HCV genotype 1, 2 or 3.	n=147 (planned); 18-70 years of age; HCV genotype 1, 2 or 3; treatment naive.
Schedule	Randomised to **Part 1** Arms 1-4; genotype 2 or 3 treatment naive: sofosbuvir 400mg with RBV on weeks1-12. Participants in arms 2-4 also received peg-IFN on weeks 1-4, 1-8 and 1-12 respectively. **Part 2** Arm 5; genotype 2 or 3 treatment naïve: sofosbuvir 400mg on weeks 1-12. Arm 6; genotype 2 or 3 treatment naïve: sofosbuvir 400mg with RBV and peg-IFN on weeks 1-8. Arm 7; genotype 1 treatment experienced: sofosbuvir 400mg with RBV weeks 1-12. **Part 3** Arm 8; genotype 1 treatment naive and arm 9; genotype 1 treatment experienced: sofosbuvir 400mg and RBV weeks 1-8. **Part 4** Arm10; genotype 2 and 3 treatment naive: sofosbuvir 400mg and RBV weeks 1-8. Arm 11; genotype 2 or 3 treatment naïve: sofosbuvir 400mg and RBV weeks 1-8. Arms 12 and 13; genotype 1 treatment experienced and treatment naive: sofosbuvir 400mg with RBV and GS5885 on weeks 1-12.	Randomised to sofosbuvir 200mg, 400mg or placebo, all in combination with peg-IFN and RBV for 12 weeks. Genotype 1 participants with early rapid virologic response received additional 12 weeks of peg-IFN and RBV, those with no early response received a further 36 weeks of peg-IFN and RBV. Genotype 2 and 3 participants received no additional treatment following the initial 12 week treatment period.

[b] Gilead Sciences is also developing GS 5885, an orally-active NS5A protein inhibitor, for the treatment of HCV infections.

Follow-up	Active treatment period of up to 12 week, follow-up 48 weeks.	Active treatment period of up to 25-48 weeks.
Primary outcome/s	Safety and tolerability.	Safety and tolerability.
Secondary outcome/s	HCV RNA a week or 12, HCV RNA throughout study period, SVR at week 12, resistance, duration of peg-IFN therapy, pharmacokinetics.	HCV RNA over 12 weeks, rapid virologic response, complete early virologic response.
Adverse effects (AEs)	-	Sofosbuvir was generally safe and well tolerated. AE profile similar to peg-IFN and RBV therapy.
Expected reporting date	Estimated study completion Dec 2013.	Study completion date previously reported as Apr 2011.

Trial	NCT01054729; sofosbuvir 100mg, 200mg or 400mg vs placebo both in combination with peg-IFN and RBV; phase II.	NCT01559844; sofosbuvir with RBV; phase II.
Sponsor	Gilead Sciences.	Gilead Sciences.
Status	Complete, but unpublished.	Ongoing.
Source of information	Trial registry[33], manufacturer.	Trial registry[34], manufacturer.
Location	USA and Puerto Rico.	USA, New Zealand and Spain.
Design	Randomised, placebo-controlled.	Uncontrolled, open-label.
Participants	n=64 (planned); 18-65 years of age; HCV genotype 1.	n=40 (planned); >18 years of age; chronic HCV infection; meet MILAN criteria[c];undergoing liver transplant for hepatocellular carcinoma secondary to HCV.
Schedule	Randomised to Arm 1: sofosbuvir 100mg or placebo once daily for 28 days, both with peg-IFN and RBV for 48 weeks. Arm 2: sofosbuvir 200mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks. Arm 3: sofosbuvir 400mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks.	Sofosbuvir 400mg once daily with RBV.
Follow-up	Active treatment period 48 weeks, follow-up 48 weeks.	Active treatment period 48 weeks, follow-up 48 weeks.
Primary outcome/s	Safety and tolerability.	Post-transplant virologic response.
Secondary outcome/s	HCV RNA.	Sustained SVR, safety and tolerability, HCV viral kinetic, absence of liver HCV RNA, no-tumour MELD score[d], serum biochemical parameters.
Key results	Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile. Clinical efficacy was higher in the 200mg and 400mg dosing groups.	-

[c] The Milan criteria state that a patient is selected for transplantation when they have one lesion smaller than 5 cm, up to 3 lesions smaller than 3 cm, no extra hepatic manifestations and no vascular invasion.

[d] MELD a numerical scale used for adult liver transplant candidates.

Adverse effects (AEs)	Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile.	-
Expected reporting date	Study completion previously reported as Aug 2011.	Estimated study completion Mar 2013.

COST and IMPACT

COST

The cost of sofosbuvir is not yet known. The costs of currently licensed treatments are[35,e]:

Drug	Dose	12 week cost	48 week cost
Peginterferon alfa-2a	180µg SC once weekly.	£1,492	£5,971
Peginterferon alfa-2b	100µg SC once weekly.	£1,595	£6,380
Ribavirin	1,200mg daily.	£1,110	£4,440
Telaprevir	2,250mg daily.	£22,398	-
Boceprevir	2,400mg daily	£8,400	£22,400[f]

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☑ Other
- ☐ No impact identified

Impact on Services

- ☐ Increased use of existing services
- ☑ Decreased use of existing services
- ☐ Re-organisation of existing services: reduced treatment time.
- ☐ Need for new services
- ☐ Other:
- ☐ None identified

Impact on Costs

- ☑ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs:
- ☑ Other reduction in costs: potential for reduced clinic time and adverse events.
- ☐ Other:
- ☐ None identified

Other Issues

- ☐ Clinical uncertainty or other research question identified:
- ☑ None identified

[e] Based on average weight 77.9kg (men and women).
[f] Indicated for 32 weeks of treatment.

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