Peginterferon lambda-1a for hepatitis C

SUMMARY

Peginterferon lambda-1a is intended for the treatment of hepatitis C virus (HCV) infection in adult patients who are treatment naïve or have relapsed to prior pegylated alfa interferon, including patients with compensated cirrhosis without evidence of portal hypertension, and in patients with HIV co-infection. If licensed, peginterferon lambda-1a would offer an additional treatment option for patients with HCV infection. Peginterferon lambda-1a is a recombinant pegylated interferon lambda-type compound which acts as an agonist for the interleukin-29 (IL-29) receptor, mediating antiviral activity through a receptor distinct from those used in the interferon alfa pathway. Currently, peginterferon lambda-1a does not have Marketing Authorisation in the UK for any indication.

The true incidence of HCV infection is difficult to establish, as approximately 86% of infected individuals are unaware of their infection status. Estimates indicate that 160,000 adults may be chronically infected with hepatitis C in England, equating to 0.4% of the adult population. Prevalence in England and Wales ranges between 0.6% and 1.2% of the population. In 2010, there were 10,380 HCV diagnoses in the UK. Estimates suggest that by 2020, if left untreated, around 16,000 people will be living with HCV-related cirrhosis or hepatocellular carcinoma in England.

There are several current and emerging treatment options for HCV infection dependent on genotype and co-infection, including a number of combination regimens. Currently licensed treatments include peginterferon alfa-2a or 2b with ribavirin and telaprevir or boceprevir. Simeprevir and sofosbuvir are currently under NICE appraisal for HCV. Peginterferon lambda-1a is currently undergoing numerous phase III clinical trials comparing its effect with and/or in combination with existing comparators. Key outcomes across the phase III trials include virologic responses and treatment-emergent adverse events. The first of these trials is expected to complete in December 2014.
TARGET GROUP

- Hepatitis C virus (HCV) infection; chronic; genotypes 1 to 4; adults; treatment naïve or relapsed to prior pegylated alfa interferon treatment; including patients with compensated cirrhosis without evidence of portal hypertension and patients with HIV co-infection.

TECHNOLOGY

DESCRIPTION

Peginterferon lambda-1a (BMS-914143) is a recombinant pegylated interferon lambda-type compound which acts as an agonist for the interleukin-29 (IL-29) receptor, mediating antiviral activity through a receptor distinct from those used in the interferon alfa pathway. It is intended for the treatment of HCV infection in adults. Peginterferon lambda-1a is administered subcutaneously (SC) and in several phase III clinical trials, a dose of 180µg was administered.21,22,23,24,25,26 Duration of treatment is expected to be in the range 24-48 weeks and dependent upon patient genotype infection and co-infection status.

Peginterferon lambda-1a does not currently have Marketing Authorisation in the EU for any indication. Peginterferon lambda-1a is currently in phase II clinical trials for hepatitis B.

INNOVATION and/or ADVANTAGES

If licensed, peginterferon lambda-1a will offer an additional treatment option for adults with HCV.

DEVELOPER

Bristol-Myers Squibb (EU/UK licence holder); ZymoGenetics.

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 nine different HCV genotypes; genotype 3 is the most common in the UK and responsible for 50% of cases, closely followed by genotype 1, which is responsible for 46% of cases1,2, and until recently was the most resistant to treatmenta. The virus is acquired primarily through percutaneous exposure to contaminated blood3. Most acute infections with HCV are asymptomatic with only 20% developing overt symptoms4. Approximately 80% of people who are infected go on to develop chronic HCV, symptoms of which include malaise, weakness and anorexiaa. Chronic HCV is categorised as mild, moderate or severe depending on the extent of liver damagea. Approximately 30% of chronically infected people develop cirrhosis within 20-30 years, and some of these develop

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a Expert personal opinion.
hepatocellular carcinoma (HCC)\textsuperscript{3}. End-stage liver disease or HCC may require liver transplantation\textsuperscript{3}. Factors known to increase the rate of progression include age, ethnicity, male sex, excessive alcohol consumption and HIV co-infection\textsuperscript{5,6}.

**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, as approximately 86% of infected individuals are unaware of their infection status\textsuperscript{7}. Recent estimates suggest that in England, there are around 160,000 individuals who are chronically infected with HCV, equating to 0.4% of the adult population\textsuperscript{8}. Prevalence in England and Wales ranges between 0.6% to 1.2% of the population and in 2010, there were 10,380 new diagnoses in the UK\textsuperscript{7}. Estimates suggest that by 2020, if left untreated, around 15,840 individuals will be living with HCV-related cirrhosis or HCC in England\textsuperscript{2}. An estimated 30.6% of people with HCV infection currently receive antiviral treatment\textsuperscript{7}.

One hundred and ninety-four deaths from chronic viral hepatitis C were registered in England and Wales during 2012 (ICD-10 B18.2)\textsuperscript{9}. In 2012-13, there were 2,265 admissions for chronic viral hepatitis C (ICD-10 B18.2) in England, resulting in 2,746 bed-days and 2,452 finished consultant episodes\textsuperscript{10}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

CURRENT TREATMENT OPTIONS

The standard treatment for HCV infection is combination therapy with pegylated interferon alfa and ribavirin given for varying periods according to genotype; this is successful in clearing the virus in between 40% and 80% of those treated\(^5\). Patients with genotype 1 are treated with triple combination therapy (pegylated interferon and ribavirin with the addition of one of the first generation protease inhibitors, telaprevir or boceprevir)\(^{16,17}\) for a duration influenced by pre-treatment factors (including cirrhosis) and on-treatment response to therapy\(^{18}\). Simeprevir, a second generation protease inhibitor (currently under NICE appraisal) may become standard of care, replacing telaprevir and boceprevir in triple combination therapy\(^{19}\). Similarly, sofosbuvir is undergoing NICE appraisal for HCV infection (genotypes 1 and 4)\(^{20}\). All patients with chronic HCV infection are considered for therapy, irrespective of the stage of their disease\(^5\).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial registry(^{21}).</td>
<td>Bristol-Myers Squibb.</td>
<td>Ongoing.</td>
<td>EU (incl UK), USA, Canada, Brazil and Russian Federation.</td>
<td>Part A: single arm; part B randomised, active-controlled.</td>
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<tr>
<td>Trial registry(^{22}).</td>
<td>Bristol-Myers Squibb.</td>
<td>Ongoing.</td>
<td>EU (incl UK), USA, and other countries.</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Trial registry(^{23}).</td>
<td>Bristol-Myers Squibb.</td>
<td>Ongoing.</td>
<td>EU (incl UK), USA and other countries.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=636; aged 18 to 70 years; chronic hepatitis C, genotype 1 (genotype 1b capped at 50% of naïve subjects); naïve to previous HCV therapy or relapsed/discontinued on previous therapy (capped at 20%); HCV RNA ≥ 100,000IU/ml; includes compensated cirrhosis (capped at 10%); HIV and hepatitis B surface antigen negative.</td>
<td>n=450 (planned); aged 18 years and older; HCV infection, genotype 1b; treatment naïve or evidence of relapse; HCV RNA ≥ 100,000IU/ml; includes compensated cirrhosis.</td>
<td>n=880; aged 18 years and older; chronic hepatitis C, genotypes 2 and 3; treatment naïve.</td>
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<tr>
<td>Schedule</td>
<td>Part A: Subjects receive 180µg peginterferon lambda-1a SC, once weekly for 24 or 48 weeks (response-dependent) with 1,000mg or 1,200mg (weight-based) ribavirin orally, twice daily for 24 or 48 weeks (response-dependent) and 750mg telaprevir orally, three times daily for 12 weeks. Randomised to Arm 1: 180µg peginterferon lambda-1a SC, once weekly for 24 or 48 weeks (response-dependent) with 1,000mg or 1,200mg (weight-based) ribavirin orally, twice daily for 24 or 48 weeks (response-dependent) and 750mg telaprevir orally, three times daily for 12 weeks. Arm 2: 180µg peginterferon alfa-2a SC, once weekly for 24 or 48 weeks (response-dependent) with 1,000mg or 1,200mg (weight-based) ribavirin orally, twice daily for 24 or 48 weeks (response-dependent) and 750mg telaprevir orally, three times daily for 12 weeks.</td>
<td>Randomised to 180µg peginterferon lambda-1a SC, once weekly for 24 weeks, with 60mg daclatasvir orally, once daily for 12 weeks; or 180µg peginterferon alfa-2a SC, once weekly for 24 to 48 weeks (response-dependent), with 375mg telaprevir orally, three times a day for 12 weeks; both in combination with 1,000mg to 1,200mg total daily dose (weight-based) ribavirin orally, twice daily for 24 weeks.</td>
<td>Randomised to: Arm 1: 180µg peginterferon lambda-1a SC, once weekly for 24 weeks with 400mg ribavirin orally, twice daily for 24 weeks and placebo orally, once daily for 12 weeks. Arm 2: 180µg peginterferon lambda-1a SC, once weekly for 12 weeks with 400mg ribavirin orally, twice daily for 12 weeks and 60mg daclatasvir orally, once daily for 12 weeks. Arm 3: 180µg peginterferon alfa-2a SC, once weekly for 24 weeks with 400mg ribavirin orally, twice daily for 24 weeks and placebo orally, once daily for 12 weeks.</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period for 24 or 48 weeks, follow-up period 48 weeks.</td>
<td>Active treatment period 24 to 48 weeks, follow-up period 72 weeks.</td>
<td>Active treatment period for 12 weeks, follow-up for 24 weeks.</td>
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</table>
### Primary outcome/s

**Part A:** proportion of subjects achieving eRVR\(^b\) at 4 and 12 weeks, treatment safety.

**Part B:** proportion of subjects achieving SVR12\(^c\).

### Secondary outcome/s

**Part A:** proportion of subjects with SVR12 and SVR24\(^d\).

**Part B:** proportion of subjects with SVR12 and SVR24, eRVR; cytopenic abnormalities, flu-like symptoms and musculoskeletal symptoms.

### Expected reporting date

<table>
<thead>
<tr>
<th>Study completion date</th>
<th>Study completion date</th>
<th>Study completion date</th>
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<tbody>
<tr>
<td>reported as January 2016.</td>
<td>reported as April 2015.</td>
<td>reported as December 2014.</td>
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### Trial

<table>
<thead>
<tr>
<th>Trial</th>
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<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01754974, AI452-033, 2012-003508-11, BASIS; peginterferon lambda-1a or peginterferon alfa-2a, both with ribavirin; phase III.</td>
<td>Bristol-Myers Squibb.</td>
<td>Suspended participant recruitment.</td>
<td>Trial registry(^{24}).</td>
<td>Czech Republic, Mexico and Republic of Korea.</td>
</tr>
<tr>
<td>NCT01741545, AI452-030, 2012-003463-22, MAGNITUDE; HCV with haemophilia; peginterferon lambda-1a with ribavirin and daclatasvir; phase III.</td>
<td>Bristol-Myers Squibb.</td>
<td>Ongoing.</td>
<td>Trial registry(^{25}).</td>
<td>EU (not UK), USA, Russia Federation and Australia.</td>
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<tr>
<td>NCT01866930, AI452-032, 2012-003280-22, DIMENSION; HCV with HIV; peginterferon lambda-1a with ribavirin and daclatasvir; phase III.</td>
<td>Bristol-Myers Squibb.</td>
<td>Ongoing.</td>
<td>Trial registry(^{26}).</td>
<td>EU (not UK), USA, Canada, Argentina, Mexico and Russian Federation.</td>
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</table>

### Design

| Randomised, active- | Non-randomised. | Non-randomised. |

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\(^b\) Extended rapid virologic response – defined as undetectable HCV RNA levels at week 4 through to week 12.

\(^c\) Sustained virologic response at 12 weeks.

\(^d\) Sustained virologic response at 24 weeks.

\(^e\) Rapid virologic response – defined as undetectable HCV RNA levels after 4 weeks of treatment.
| Participants | n=45 (suspended); aged 18 to 70 years; chronic hepatitis C, genotype 1; HCV RNA ≥ 100,000IU/ml, no cirrhosis in previous 3 years; treatment naive. | n=50 (planned); aged 18 years and older; male; severe haemophilia (<1% factor activity level); HCV infection; no previous treatment with an interferon. | n=300 (planned); aged 18 years and older; HCV genotype 1, 2, 3 or 4; treatment naïve; HCV RNA ≥ 10,000IU/ml; HIV-1 infection (approximately 200 patients receiving HAART and approximately 100 patients not receiving HAART); HAART subjects HIV RNA < 40 copies/ml at screening and <200 copies/ml at 8 weeks prior to screening; CD4 cell count at screening ≥ 100 cells/µl or ≥ 300 cells/µl if receiving HAART; hepatitis B surface antigen negative; BMI 18 to 35kg/m²; includes patients with compensated cirrhosis. |
| Schedule | Randomised to 180µg peginterferon lambda-1a SC, once weekly; or 180µg peginterferon alfa-2a SC, once weekly; both in combination with 1,000mg or 1,200mg (weight-based) ribavirin orally, twice daily for 48 weeks. | Patients receive: Cohort A (genotypes 2 and 3): 180µg peginterferon lambda-1a SC, once weekly for 12 weeks with 200mg ribavirin orally, twice daily for 24 weeks and 60mg daclatasvir orally, once daily for 12 weeks. Cohort B (genotypes 1b and 4): 180µg peginterferon lambda-1a SC, once weekly for 24 weeks with 200mg ribavirin orally, twice daily for 24 weeks and 60mg daclatasvir orally, once daily for 12 weeks. | Patients receive: Cohort A (genotypes 2 and 3): 180µg peginterferon lambda-1a SC, once weekly for 24 weeks with 200mg ribavirin orally, twice daily for 24 weeks and 30mg, 60mg or 90mg (depending on concomitant HIV regimen) daclatasvir orally, once daily for 12 weeks. Cohort B (genotypes 1b and 4): 180µg peginterferon lambda-1a SC, once weekly for 24 or 48 weeks with 200mg (or weight-dependent dose) ribavirin orally, twice daily for 24 or 48 weeks and 30mg, 60mg or 90mg (depending on concomitant HIV regimen) daclatasvir orally, once daily for 12 weeks. |
| Follow-up | Active treatment period 48 weeks, follow-up period up to 48 weeks. | Active treatment for 12 or 24 weeks, follow-up period 24 weeks, subjects with AEs followed-up for 72 weeks. | Active treatment for 24 or 48 weeks, follow-up period 48 weeks. |
| Primary | Proportion of subjects with treatment emergent | Proportion of subjects | Proportion of subjects |

f Highly active antiretroviral therapy.
Cytopenic abnormalities.

Proportion of subjects achievingSVR24, RVR, on-treatment serious AEs, dose reductions through end of treatment, discontinuation due to AEs, on-treatment interferon associated symptoms.

Proportion of subjects achieving a RVR; cEVR; HCV RNA < LLOQ target ‘not detected’; treatment emergent cytopenic abnormalities; on-treatment interferon-associated symptoms; SVR24.

Proportion of subjects achieving a RVR and eRVR; HCV RNA < LLOQ target detected or not detected (SVR24); treatment emergent cytopenic abnormalities during treatment period; on-treatment interferon-associated symptoms; deaths, serious AEs; AEs; change from baseline in CD4 cell count, lymphocyte cell count and platelet count.

| Expected reporting date | Study completion date reported as May 2015. | Study completion date reported as March 2017. | Study completion date reported as January 2016. |

**ESTIMATED COST and IMPACT**

**COST**

The cost of peginterferon lambda-1a is not yet known. The cost of other selected treatments for HCV infection are summarised below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>12 week cost</th>
<th>24 week cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a (Pegasys)</td>
<td>180µg SC, once weekly</td>
<td>£1,493</td>
<td>£2,986</td>
</tr>
<tr>
<td>Peginterferon alfa-2b (VirafeonPeg)</td>
<td>100µg-120µg SC, once weekly</td>
<td>£1,595-£1,914</td>
<td>£3,190-£3,828</td>
</tr>
<tr>
<td>Ribavirin (Rebetol)</td>
<td>1,000mg oral, daily</td>
<td>£803.45</td>
<td>£1,607</td>
</tr>
<tr>
<td>Telaprevir (Incivo)</td>
<td>2,250mg oral, daily</td>
<td>£22,398</td>
<td>n/a</td>
</tr>
<tr>
<td>Boceprevir (Victrelis)</td>
<td>2,400mg oral, daily</td>
<td>£8,400</td>
<td>£16,800</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi)</td>
<td>400mg oral, daily</td>
<td>£34,983</td>
<td>£69,966</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 Health and Social Care Services**
  - Increased use of existing services
  - Decreased use of existing services
  - Re-organisation of existing services
  - Need for new services
  - Other:
    - None identified

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9 Complete early virologic response – defined as undetectable HCV RNA levels after 12 weeks of treatment.

h Lower Limit of Quantification.

1 Average adult bodyweight (Health Survey for England (HSE) 2010: adults 77.9kg.
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other: uncertain unit cost compared to existing treatments
- None identified

Other Issues

- Clinical uncertainty or other research question identified: Interferon-free regimens are emerging and are generally more effective and better tolerated than interferon-containing treatment regimens. In this case, it means that there may be no role for interferons in the treatment of HCV in the intermediate future. Interferons may have a more persistent role in poorer countries because they will be relatively inexpensive compared to the newer drugs in development.
- None identified

REFERENCES

1 Mohsen A and Norris S. Hepatitis C (Chronic). Clinical Evidence 2010;02:921.
7 Patruni B and Nolte E. Hepatitis C. A projection of the healthcare and economic burden in the UK. The Hepatitis C Trust 2013. 
9 Office for National Statistics. Mortality statistics: deaths registered in 2012 (series DR) Table 5. 
www.ons.gov.uk

J Expert personal opinion.


26 ClinicalTrials.gov. Efficacy and safety study of pegylated interferon lambda-1a with ribavirin and daclatasvir, to treat naïve subjects with chronic HCV genotypes 1, 2, 3 and 4 who are co-infected with HIV (DIMENSION). http://www.clinicaltrials.gov/ct2/show/NCT01866930?term=NCT01866930&rank=1 Accessed 28 May 2014.