Tenofovir alafenamide monotherapy for hepatitis B

SUMMARY

Tenofovir alafenamide is intended to be used as monotherapy for the treatment of chronic hepatitis B. Tenofovir alafenamide is a nucleotide analogue reverse transcriptase inhibitor (NtRTI) and a prodrug of tenofovir, with a potentially greater antiviral activity compared to the existing tenofovir preparation, tenofovir disoproxil fumarate. If licensed, tenofovir alafenamide monotherapy will provide an additional oral treatment option for patients with chronic hepatitis B.

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is the most common chronic viral infection in the world and an estimated two billion people are infected, and more than 350 million people are chronic carriers of the virus. The likelihood that infection with the virus becomes chronic depends upon the age at which a person becomes infected: 80-90% of infants infected during the first year of life and 30-50% of children infected before the age of six develop chronic infection, whilst 20-30% of adults who are chronically infected will develop cirrhosis and/or liver cancer. In the UK, approximately 78,000 people are diagnosed with chronic hepatitis B each, of whom 5% receive antiviral treatment.

Chronic hepatitis B can be treated with specific antiviral agents and these treatments can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival. Tenofovir is currently in two phase III trials comparing its effects on circulating hepatitis B viral DNA levels against treatment with tenofovir disoproxil fumarate. These trials are expected to complete in 2015.
TARGET GROUP

- Hepatitis B: chronic; treatment naïve and treatment experienced patients.

TECHNOLOGY

DESCRIPTION

Tenofovir alafenamide (GS-7340, GS7340, GS 7340, GS 7340-02) is a nucleotide analogue reverse transcriptase inhibitor (NtRTI) and a prodrug of tenofovir with a potentially greater antiviral activity compared to the existing tenofovir preparation, tenofovir disoproxil fumarate. Tenofovir has poor oral bioavailability and cellular permeability. Tenofovir alafenamide is designed to be stable in plasma and then be rapidly converted into tenofovir once inside cells. Tenofovir alafenamide provides high levels of the active drug in target cells (e.g., hepatocytes and lymphoid cells) at lower doses than tenofovir disoproxil fumarate. Reduced systemic exposure to tenofovir offers the potential for an improved safety profile e.g. reduced bone and renal adverse events. In phase III clinical trials, tenofovir alafenamide is administered as monotherapy, orally at 25mg once daily for 96 weeks.

Tenofovir alafenamide is not currently licensed for any other indication. It is in phase III clinical trials for HIV-1 in combination with other antiviral agents.

INNOVATION and/or ADVANTAGES

If licensed, tenofovir alafenamide monotherapy will provide an additional oral treatment option for patients with chronic hepatitis B.

DEVELOPER

Gilead Sciences.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Hepatitis B virus infection is the most common chronic viral infection in the world. An estimated two billion people are infected, and more than 350 million are chronic carriers of the virus. Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. The virus can provoke an acute illness characterised by nausea, malaise, abdominal pain and jaundice, but more commonly leads to a chronic infection that is associated with an increased risk of chronic liver disease and hepatocellular carcinoma. The likelihood that infection with the virus becomes chronic depends upon the age at which a person becomes infected: 80-90% of infants infected during the first year of life and 30-50% of children infected before the age of six years develop chronic infection. In contrast, less than 5% of otherwise healthy people who are infected as adults will develop chronic infection, and 20-30% of adults who are chronically infected will develop cirrhosis and/or liver cancer. The
virus is transmitted through contact with the blood or other body fluids of an infected person (including vertical transmission from mother to baby). Hepatitis B is also an important occupational hazard for health workers; although it can be prevented by a currently available safe and effective vaccine.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

In the UK, approximately 1 in 350 people are thought to be chronically infected with hepatitis B. In some inner city areas, with high percentages of people from parts of the world where the virus is common, as many as 1 in 60 pregnant women may be affected. A study of laboratory data in England and Wales estimated that the annual incidence of hepatitis B is around 7.4 per 100,000 people. This equates to around 3,700 new infections per year, and around 270 new cases of chronic hepatitis B per year. Approximately 300,000 people have chronic hepatitis B in England and there are about 6,400 new cases diagnosed each year. An estimated 78,000 in the UK people are known to be living with chronic hepatitis B, and approximately 5% of these (3,900) receive antiviral treatment each year.

In 2013-14, there were 303 hospital admissions due to hepatitis B (ICD-10 B16-16.9) in England, resulting in 1,326 bed days and 465 finished consultant episodes. In 2013, 34 deaths were registered in England due to hepatitis B. The population likely to be eligible to receive tenofovir alafenamide could not be estimated from available sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE public health guidance. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (PH43). December 2012.
CURRENT TREATMENT OPTIONS

Chronic hepatitis B can be treated with specific antiviral agents. Treatment can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival⁹.

The current treatment options for chronic hepatitis B are:
- Lamivudine, an oral nucleoside analogue reverse transcriptase inhibitor.
- Interferon alfa (IFNo) and peginterferon alfa-2a (pegIFNa) (intravenous or subcutaneous).
- Tenofovir disoproxil fumarate.
- Adefovir dipozoxil, an oral nucleotide reverse transcriptase inhibitor (effective in lamivudine-resistant and IFNα/pegIFNa-resistant chronic hepatitis B).
- Entecavir, an oral nucleoside analogue DNA polymerase and reverse transcriptase inhibitor, licensed for the treatment of HBV with compensated liver disease.
- Telbivudine, an oral L-nucleoside analogue DNA polymerase inhibitor.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01940471; tenofovir alafenamide vs tenofovir disoproxil fumarate; phase III.</th>
<th>NCT01940341; tenofovir alafenamide vs tenofovir disoproxil fumarate; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Gilead Sciences.</td>
<td>Gilead Sciences.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry⁵.</td>
<td>Trial registry¹⁵.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=864 (planned): aged ≥18 years; documented evidence of chronic hepatitis B virus (HBV) infection; hepatitis B e antigen (HBeAg)-positive; screening HBV DNA ≥2x10⁴IU/ml, screening serum alanine aminotransferase (ALT) level &gt;60U/L (males) or &gt;38U/L (females); treatment naïve patients (&lt;12 weeks of treatment with any nucleoside or nucleoside analogue) or treatment experienced patients (≥12 weeks of previous treatment with any nucleoside or nucleotide analogue); previous treatment with interferon (pegylated or non-pegylated) ended 6 months before screening; adequate renal function; normal ECG.</td>
<td>n=390 (planned): aged ≥18 years; documented evidence of chronic HBV infection; HBeAg-negative; screening HBV DNA ≥2x10⁴IU/ml, screening serum alanine ALT level &gt;60U/L (males) or &gt;38U/L (females); treatment naive patients (&lt;12 weeks of treatment with any nucleoside or nucleoside analogue) or treatment experienced patients (≥12 weeks of previous treatment with any nucleoside or nucleotide analogue); previous treatment with interferon (pegylated or non-pegylated) ended 6 months before screening; adequate renal function; normal ECG.</td>
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<td>Schedule</td>
<td>Randomised to tenofovir alafenamide, 25mg orally once a day for 96 weeks or tenofovir disoproxil fumarate, 300mg orally once a day for 96 weeks.</td>
<td>Randomised to tenofovir alafenamide, 25mg orally once a day for 96 weeks, or tenofovir disoproxil fumarate, 300mg orally once a day for 96 weeks.</td>
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<td>Follow-up</td>
<td>Active treatment for 96 weeks, follow-up to week 144.</td>
<td>Active treatment for 96 weeks, follow-up to week 144.</td>
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</table>
Primary outcome/s | Achievement of HBV DNA < 29IU/ml at 48 weeks. | Achievement of HBV DNA < 29IU/ml at 48 weeks.  
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Secondary outcome/s | Proportion of patients with HBeAg loss with seroconversion to hepatitis B e antibody at 48 weeks; change in hip and spine bone mineral density; change in serum creatinine to week 48. | Change in hip and spine bone mineral density; change in serum creatinine to week 48.  
Expected reporting date | Study completion date reported as November 2015. | Study completion date reported as September 2015.  

**ESTIMATED COST and IMPACT**

**COST**

The cost of tenofovir alafenamide is not yet known, however tenofovir disoproxil fumarate for its current licensed indication costs £204.39 for a 30-tablet pack.

**IMPACT - SPECULATIVE**

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

**Impact on Health and Social Care Services**
- Increased use of existing services
- Re-organisation of existing services
- Other: Decreased use of existing services
- Need for existing services
- Other: None identified

**Impact on Costs and Other Resource Use**
- Increased drug treatment costs
- Other increase in costs:
- Other: None identified
- Reduced drug treatment costs
- Other reduction in costs:
- None identified

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

**REFERENCES**

11 National Institute for Health and Care Excellence. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. NICE public health guideline PH43. London: NICE; June 2013.