Simtuzumab for liver fibrosis in patients with non-alcoholic steatohepatitis or primary sclerosing cholangitis

LAY SUMMARY

Non-alcoholic steatohepatitis is a common liver disease in which the liver becomes inflamed and fat builds up in the liver. The damage gets worse over time, and in later stages of the disease, scar tissue forms as a result of the inflammation (fibrosis); this may cause liver failure. Primary sclerosing cholangitis is a rare long-term liver disease in which the tubes that carry bile into the bowel (bile ducts) become progressively narrower due to inflammation and scarring.

Simtuzumab is a new drug for the treatment of liver fibrosis in patients with non-alcoholic steatohepatitis or primary sclerosing cholangitis. Simtuzumab can either be given by an injection (under the skin) or in a drip (directly into the vein).

If simtuzumab is licensed for use in the UK, it will offer a new treatment for liver fibrosis in non-alcoholic steatohepatitis and primary sclerosing cholangitis patients.

NIHR HSRIC ID: 9251
TARGET GROUP

- Liver fibrosis secondary to non-alcoholic steatohepatitis or primary sclerosing cholangitis.

TECHNOLOGY

DESCRIPTION

Simtuzumab (AB-0024; anti-LOXL2 monoclonal antibody; GS-6624; AB-0023) is a humanised monoclonal antibody that inhibits lylsl oxidase-like 2, an enzyme which plays a role in the formation of pathologic stroma in tumours and is involved in the maintenance of tissues. Simtuzumab also inhibits critical growth factors such as vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF-1), connective tissue growth factor (CTGF) and transforming growth factor-β1 (TGFβ1). In a phase IIb clinical trial, simtuzumab was administered by subcutaneous (SC) injection at 75mg or 125mg once weekly for up to 240 weeks. Simtuzumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, simtuzumab will offer an additional treatment option for liver fibrosis secondary to non-alcoholic steatohepatitis or primary sclerosing cholangitis.

DEVELOPER

Gilead Sciences.

AVAILABILITY, LAUNCH OR MARKETING

Simtuzumab is in phase II clinical trials.

PATIENT GROUP

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in many developed countries. Approximately one fifth to one third of patients with NAFLD will develop non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis, putting patients at risk of liver failure-related complications.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterised by the development of multifocal bile duct strictures that can lead to liver fibrosis and subsequent cirrhosis. The bile ducts become progressively narrower due to the inflammation and fibrosis, and the tract can become obstructed. The aetiopathogenesis of PSC is poorly understood; although it is thought to be an immune-mediated disease because of the strong associations with immune response genes and high prevalence of autoantibodies seen in patients with PSC. Interaction with intestinal microbiota may also
be important\textsuperscript{a}. Inflammatory bowel disease (IBD), usually ulcerative colitis, is associated with PSC in 65-90\% of cases\textsuperscript{4}.

Fibrosis is a common pathological feature of chronic liver disease; it results from unregulated wound-healing and is characterised by the progressive replacement of functional hepatic tissue with highly cross-linked collagen I/III-rich extracellular matrix\textsuperscript{5}. Initially a fibrous expansion occurs in portal areas, this is followed by a few bridges or septa forming, the final stage before cirrhosis is known as severe fibrosis and is characterised by the presence of numerous bridges or septa with occasional nodules\textsuperscript{7}.

### NHS or GOVERNMENT PRIORITY AREA


### CLINICAL NEED and BURDEN OF DISEASE

The prevalence of NAFLD in the UK is about 33\%\textsuperscript{8}. The risk of NAFLD is increased by obesity or overweight, type 2 diabetes, high blood pressure, high cholesterol, age over 50 years and smoking. NASH is also a common condition, affecting up to 5\% of the UK population (approximately 3.4 million people)\textsuperscript{9}. Between 10\% and 30\% of patients with NAFLD have NASH\textsuperscript{10}. NASH cirrhosis is now the third commonest indication for liver transplantation in the USA, and accounted for 12\% of patients listed for transplantation in the UK in 2009\textsuperscript{7}.

PSC is a less common liver disease, with an incidence of 1.3 per 100,000\textsuperscript{5}. The prevalence in the UK was reported as 3.85 per 100,000 in 2001\textsuperscript{11}.

In England and Wales, 1,775 deaths from fibrosis and cirrhosis of liver were registered during 2014 (ICD-10 K74)\textsuperscript{12}. In 2014, there were 5,623 admissions for fibrosis and cirrhosis of liver (K74) in England, resulting in 30,078 bed days and 8,466 finished consultant episodes\textsuperscript{13}.

The population likely to be eligible to receive simtuzumab could not be estimated from available published sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance

- NICE clinical guideline in development. Liver disease (non-alcoholic fatty [NAFLD]) (CGWAVE0692). Expected July 2016.

\textsuperscript{a} Expert personal opinion.
CURRENT TREATMENT OPTIONS

Currently there are no specific drug therapies available for NAFLD, NASH or PSC. The bile acid ursodeoxycholic acid is widely used in the treatment of PSC, although there is no controlled trial evidence showing benefit. Patients with NAFLD and NASH are advised to make healthy lifestyle choices to improve their predisposing conditions such as obesity, high blood pressure, diabetes and raised serum cholesterol. Lifestyle changes which are of benefit include weight loss, partaking in regular exercise, reduction of alcohol intake and stopping smoking. Coffee drinking appears protective for NAFLD and PSC. Worsening liver fibrosis from whichever cause may lead to the development of cirrhosis, which is irreversible, and may lead, in turn, to a progressive loss of liver function. A liver transplant may be required in severe cases.

EFFICACY and SAFETY

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<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
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<td>EU (incl UK), USA, Canada and Puerto Rico</td>
<td>EU (incl UK), USA, and Canada.</td>
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<tr>
<td>Participants</td>
<td>n=222 (planned); aged 18-65 yrs; chronic liver</td>
<td>n=259 (planned); aged 18-65 yrs; compensated liver</td>
<td>n=235 (planned); aged 18-70 yrs; chronic cholestatic</td>
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b Expert personal opinion.
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<th>Disease due to NASH; stage 3-4 fibrosis.</th>
<th>Cirrhosis due to NASH; Ishak fibrosis stage ≥ 5.</th>
<th>Liver disease due to primary sclerosing cholangitis.</th>
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**Schedule**
- Randomised to simtuzumab 75mg SC once a wk; or simtuzumab 125mg SC once a wk; or placebo SC injection once a wk. This is followed by an optional open label phase where all trial participants receive simtuzumab 125mg SC once a week.
- Randomised to simtuzumab 700mg via intravenous infusion (IV) once every 2 wks; or simtuzumab 200mg IV once every 2 wks; or placebo IV once every 2 wks. This is followed by an optional open label phase where all trial participants receive simtuzumab 700mg IV once every 2 wks.
- Randomised to simtuzumab 75mg SC once a wk; or simtuzumab 125mg SC once a wk; or placebo SC injection once a wk.

**Follow-up**
- Active treatment for up to 240 wks, follow-up for up to 480 wks plus 30 days.
- Active treatment for up to 240 wks, follow-up for up to 480 wks plus 30 days.
- Active treatment for 96 wks, follow-up 96 wks plus 30 days.

**Primary outcomes**
- Morphometric quantitative collagen on liver biopsy; event free survival (defined as time to progression to cirrhosis).
- Hepatic venous pressure gradient; event free survival (defined as time to liver-related event or death).
- Morphometric quantitative collagen on biopsy.

**Secondary outcome**
- Safety, including adverse events (AEs), extent of exposure, laboratory evaluations and immunogenicity. No quality of life measurement included in trial outcomes.
- Safety, including AEs, extent of exposure, laboratory evaluations and immunogenicity. No quality of life measurement included in trial outcomes.
- Safety, including AEs, extent of exposure, laboratory evaluations and immunogenicity. No quality of life measurement included in trial outcomes.

**Expected reporting date**
- Primary completion date reported as Sep 2016.
- Primary completion date reported as Sep 2016.
- Primary completion date reported as July 2016.

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**ESTIMATED COST and IMPACT**

### COST

The cost of simtuzumab is not yet known.

### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability: *simtuzumab would be expected to reduce the progression to cirrhosis, and hence reducing the prevalence of complications from advanced cirrhosis and the requirement for liver transplants*.\(^c\)
- Other
- No impact identified

\(^c\) Expert personal opinion.
Impact on Health and Social Care Services

- Increased use of existing services: fewer hospital admissions and fewer liver transplants.
- Decreased use of existing services
- Re-organisation of existing services: it would require nurse administration as a subcutaneous weekly injection and/or training the patients to administer the injections themselves.
- Need for new services
- Other
- None identified

Impact on Costs and Other Resource Use

- Increased drug treatment costs: expert opinion suggests simtuzumab is likely to be expensive and more expensive than oral agents which are currently in clinical trials.
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs: increased drug costs will be offset by reduction in other costs, e.g. reduced hospital admissions and liver transplants.
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified: if the clinical trials prove to be positive, then the proposed place of simtuzumab in NAFLD will be limited to those patients with advanced NASH, i.e. with evidence of fibrosis and inflammation. Vitamin E may also be of potential benefit for NASH, but has not been fully evaluated.
- None identified

REFERENCES


*d Expert personal opinion.