NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Bulevirtide for chronic hepatitis delta virus infection

NIHRIO ID	27111	**NICE ID**	10220
Developer/Company	MYR GmbH	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Bulevirtide is in clinical development for the treatment of chronic hepatitis Delta virus infection in adult patients with compensated liver disease. Hepatitis D is a viral infection of the liver that is dependent on the patient already being infected with hepatitis B virus. The co-infection is thought to be more severe and cause more damage to the liver than hepatitis B alone. Currently there are limited treatment options for the treatment of patients with chronic hepatitis D virus infection.

Bulevirtide is a synthetic protein that is designed to specifically to bind to and block, a receptor present on liver cells. This receptor is essential to hepatitis B and D viruses entering and infecting the liver cells. By blocking the entry of hepatitis D virus, bulevirtide limits the virus ability to spread and replicate, reducing the symptoms of infection. If licensed, bulevirtide will become the first-in-class potent entry inhibitor offering a new therapeutic option for patients suffering from chronic hepatitis delta virus infection for whom limited therapeutic regimens are available.

PROPOSED INDICATION

Treatment of Chronic Hepatitis Delta (CHD) virus infection in adult patients with compensated liver disease.[1]

TECHNOLOGY

DESCRIPTION

Bulevirtide (formerly Myrcludex B) is a 47-amino acid long, n-terminally myristoylated, hepatitis B virus (HBV) envelope protein derived synthetic peptide. Its mechanism of antiviral action is characterized by its highly specific binding and inactivation of the hepatocyte surface protein, sodium taurocholate co-transporting polypeptide (NTCP). It is the single representative of an entry inhibitor, a novel class of anti-HBV/hepatitis D virus (HDV) molecules. By blocking NTCP, bulevirtide prevents infection of liver cells. Bulevirtide does not directly interfere with viral production or elimination of the virus.[2] By blocking the essential entry step, the de novo infection of the liver cells is decreased, viral spread is inhibited, and the viral life cycle is disrupted. The reduction of HDV producing cells in the liver leads to control over the infection and improvement in liver inflammation. This mechanism of action offers the possibility to efficiently treat patients with chronic HDV infection.[3]

Bulevirtide is currently in clinical development for the treatment of patients with CHD. In the phase III clinical trial (NCT03852719) the drug is administered via subcutaneous injections at doses of 2 mg or 10 mg once daily for 144 weeks or 96 weeks respectively.[1]

INNOVATION AND/OR ADVANTAGES

At the time of orphan designation (June 2015) and today, no satisfactory treatment options for HDV infection are available worldwide and in the EU, which represents a significant unmet medical need.[2]

Therapeutic options for patients with CHD are limited to interferon alpha, with significant toxicities and rare curative outcome, or nucleos(t)ide analogues (NA). NAs approved for the treatment of HBV infection demonstrate only negligible antiviral effects on HDV.[4]

Bulevirtide has a novel mechanism of action and has shown antiviral effects, demonstrating a strong decline in HDV RNA serum levels and induced ALT normalisation under monotherapy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bulevirtide does not currently have Marketing Authorisation in the EU/UK for any indication.

In March 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) granted the Promising Innovative Medicine (PIM) designation to bulevirtide.[6]

In June 2015, orphan designation was granted by the European Commission to bulevirtide for the treatment of HDV infection and in May 2017 received PRIME status for chronic hepatitis D.[2,7]

In October 2018 the US FDA granted bulevirtide breakthrough therapy designation for the treatment of CHD infection.[8]

PATIENT GROUP

DISEASE BACKGROUND

Chronic hepatitis D (CHD) is a liver inflammation caused by the infection of the liver with a small, defective RNA virus, HDV. HDV is known as a 'satellite virus' of the human HBV as it requires the HBV envelope protein for assembly, release and transmission. As a consequence, HDV infection occurs as either co-infection or super-infection with HBV.[9,10]

The HBV/HDV co-infection may cause a more acute hepatitis resulting in higher rates of liver failure, hepatocellular carcinoma, cirrhosis (scarring of the liver) and portal hypertension (high blood pressure in the vessels that connect the liver and the gut) compared to HBV monoinfection.[2,11] Chronic HBV/HDV infection is considered to be the most severe form of viral hepatitis that rapidly progresses with increased risks towards liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[10,11] The liver disease associated with HDV runs a more progressive course than chronic HBV. The infection course in patients with compensated disease is mostly asymptomatic until above described complications occur.[12] However, symptoms can also include: jaundice, joint pain, abdominal pain, vomiting, loss of appetite, dark urine and fatigue.[13]

The transmission of HDV mostly occurs percutaneously or sexually through contact with infected blood or blood products. Risk factors include: chronic hepatitis B infection, lack of hepatitis B immunisation, high-risk sexual activity and intravenous drug use. HDV can also pass vertically from mother to child, through this is rare.[11,13]

CLINICAL NEED AND BURDEN OF DISEASE

CHD is very rare in the UK and is thought to be more widespread in some parts of Eastern Europe, the Middle East, Africa and South America.[14] In 2017 the annual incidence of Hepatitis B (both acute and chronic) was reported as 17.8 per 100,000 in England. According to World Health Organization (WHO), 5% of people with chronic HBV infection are co-infected with HDV.[11]

The Hospital Episode Statistics for England 2018/19 recorded a total of 21 admissions, 26 finished consultant episodes and 39 bed days for primary diagnosis chronic viral hepatitis B with delta-agent (ICD-10 code B18.0).[15]

In HBV/HDV co-infected patients are at threefold increased risk of liver cirrhosis and cancer and the 5-year mortality is twice of that of HBV monoinfection.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the EU and UK, no therapeutic regimens or drugs are approved for the treatment of HDV infection and no satisfactory treatment options are available.[2] CHD patients are usually treated with interferons or nucleoside/nucleotide analogues (NA) according to the current ESAL/AASLD guidelines.[4] Patients are routinely monitored while on therapy for serum alanine aminotransferase (ALT) level measurements, HBV and HDV viral loads, and their liver function is monitored for decompensation.[9,17,18]

If no treatment is introduced, CHD patients are at high risk to experience hepatic complications such as progression to fibrosis, cirrhosis and decompensation and the likelihood of liver transplantation increases dramatically.[13]

CURRENT TREATMENT OPTIONS

NICE recommends that patients co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) should receive a 48-week course of peg interferon alfa-2a.[17]

EASL also recommends that in HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered.[18]

PLACE OF TECHNOLOGY

If licensed, bulevirtide will offer a new treatment option for Hepatitis D patients with compensated liver disease, who currently have no effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**MYR301, NCT03852719, 2019-001213-17; Chronic Hepatitis D; high vs low dose bulevirtide; phase III.**
Sponsor	MYR GmbH
Status	Ongoing
Source of Information	Trial registry[1,19]
Location	EU (not incl UK), USA, Russia and Georgia.
Design	Randomised, open Label.
Participants	N=150 (planned); aged 18-65 years; serum anti-HDV antibody positive; positive PCR results for serum/plasma HDV RNA; Alanine transaminase level >1 x ULN, but less than 10 x ULN; Serum albumin >2.8 mg/dL.
Schedule	Randomised to; observation for 48 weeks followed by bulevirtide 10 mg/day for 96 week; bulevirtide 2 mg/day for 144 weeks; or bulevirtide 10 mg/day for 144 weeks.
Follow-up	Active treatment for 96 weeks or 144 wks, follow-up period of 96 wks
Primary Outcomes	• Combined response: Undetectable (< LLoD) hepatitis Delta virus ribonucleic acid (HDV RNA) or decrease by ⩾ 2 log10 IU/ml from baseline and ALT normalization [Time frame: 48 weeks]
Secondary Outcomes	• Undetectable HDV RNA at week 48 [Time frame: 48 weeks] • ALT normalisation at week 48 [Time frame: 48 weeks] • Undetectable HDV RNA 24 weeks after scheduled end of treatment (sustained virological response) [Time frame: 24 weeks] • Undetectable HDV RNA 48 weeks after scheduled end of treatment (sustained virological response) [Time frame: 48 weeks] • Change from baseline in liver stiffness as measured by elastography at week 48, 96, 144, 192 and 240 [Time frame: 48 weeks, 96 weeks, 144 weeks, 192 weeks, 240 weeks]
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as February 2025.

Trial	**MYR204, NCT03852433, 2019-001485-15; Chronic hepatitis D; bulevirtide or bulevirtide in combination with Peg interferon alfa-2a vs Peg interferon alfa-2a; Phase IIb**
Sponsor	MYR GmbH
Status	Ongoing
Source of Information	Trial registry[20,21]
Location	EU (not incl UK), Russia and Moldova.
Design	Randomised, open label, active-comparator.
Participants	N=175 (planned); 18-65 years; positive serum HDV antibody; positive PCR results for serum/plasma HDV RNA; Alanine transaminase level >1 x ULN, but less than 10 x ULN; Serum albumin >2.8 mg/dL; normal thyroid function.
Schedule	Randomised to; peg interferon alfa-2a for 48 weeks; bulevirtide 2 mg/day in combination with peg interferon alfa-2a for 48 weeks followed by bulevirtide 2 mg/day for 48 weeks; bulevirtide 10 mg/day in combination with peg interferon alfa-2a for 48 weeks followed by bulevirtide 10 mg/day for 48 weeks; or bulevirtide 10 mg/day for 96 weeks.
Follow-up	Active treatment for 48 weeks or 96 weeks, follow-up 48 weeks.
Primary Outcomes	• Sustained virological response 24 (SVR 24) defined as undetectable HDV RNA (HDV RNA <LLoD) at week 24 after the scheduled end of treatment (study week 120 for arms B, C and D) [Time frame: 24 weeks after the scheduled end of treatment]
Secondary Outcomes	• Number of participants with undetectable HDV RNA at week 48 (all arms), 96 (arms B, C and D) [Time frame: 48 weeks, 96 weeks] • Number of participants with combined sustained response after the scheduled end of treatment: undetectable HDV RNA or decrease by $\geqslant$ 2 log10 IU/ml from baseline and alanine aminotransferase (ALT) normalization [Time frame: 24 weeks, 48 weeks] • Number of participants with sustained virological response 48 (SVR 48) defined as undetectable HDV RNA at week 48 after the scheduled end of treatment [Time frame: 48 weeks] • Number of participants with change from baseline in liver stiffness as measured by elastography at week 48, 96, and 144 [Time frame: 48 weeks, 96 weeks, 144 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as February 2023.

Trial	**MRY-203, NCT02888106; Chronic Viral Hepatitis B with Delta-agent; Bulevirtide plus PEG IFN alfa-2a vs Bulevirtide vs PEG IFN alfa-2a vs Myrcludex plus Tenofovir; phase II**
Sponsor	Hepatera Ltd.

Status	Ongoing
Source of Information	Trial registry[22]
Location	Russia.
Design	Randomised, open label, active-comparator.
Participants	N=90 (planned); aged 18-65 years; Chronic Viral Hepatitis B with Delta-agent; HBsAg-positive; positive for anti-HDV antibodies; HDV RNA-positive; ALT ⩾ 1 x ULN and < 10 x ULN.
Schedule	Randomised to; PEG IFN alfa-2a 180 µg for 48 weeks (A); Bulevirtide 2 mg + PEG IFN alfa-2a 180 µg for 48 weeks (B); Bulevirtide 5 mg + PEG IFN alfa-2a 180 µg for 48 weeks (C); Bulevirtide 2 mg for 48 weeks (D); Bulevirtide 10 mg (10 mg once a day) + PEG-IFN alfa-2a 180 µg during 48 weeks (E) or; Bulevirtide 10 mg (5 mg twice a day) + Tenofovir during 48 weeks (F).
Follow-up	Up to 72 weeks.
Primary Outcomes	• Proportion of patients with negative HDV RNA by PCR [Time frame: 72 weeks]
Secondary Outcomes	• Proportion of patients with negative HDV RNA by PCR [Time frame: 24 and 48 weeks] • Proportion of patients with normalized ALT [Time frame: 24, 48 and 72 weeks] • Proportion of patients with combined response [Time frame: 24, 48 and 72 weeks] Combined response is defined as negative HDV RNA and ALT normalization at Weeks 24, 48, and 72. • Proportion of patients with HBsAg response [Time frame: 24, 48 and 72 weeks] HBsAg response is defined as HBsAg negativation or > 0.5 log10 decline • Proportion of patients with HBsAg negativation [Time frame: 24, 48 and 72 weeks] • Proportion of patients with negative HBV DNA by PCR [Time frame: 24, 48 and 72 weeks] • The severity of fibrosis evaluated by transient elastometry of the liver [Time frame: 48 and 72 weeks]
Key Results	Key Results from the first 4 cohorts (A-D) • The primary endpoint was defined as undetectable HDV RNA (<10IU/ml, LoD) 24 weeks of therapy (week 72) and was achieved in 0%, 53.3%, 26.7% and 6.7% in the cohorts A to D, respectively. • At the end of treatment (week 48), undetectable HDV RNA (<10IU/ml, LoD) was observed in 13.3%, 80.0%, 86.7% and 13.3% of patients in cohorts A-D, respectively. • ALT normalization was achieved in 26.7%, 26.7%, 46.7% and 73.3% at week 48 and in 10%, 53.8%, 33.3% and 23.1% at week 72 in treatment cohorts A-D, respectively. • Combination therapy of bulevirtide and PEG-IFN induced a HBsAg response (defined as >1log decline or undetectable HBsAg) in 40% (2mg Bulevirtide + PEG-IFN, incl. 26.7% HBsAg loss) and 13.3% (5mg Bulevirtide + PEG-IFN) at week 72.
Adverse effects (AEs)	-

Expected reporting date	Study completion date reported as December 2019.

Trial	**MYR-202, NCT03546621; Chronic hepatitis D; Bulevirtide with tenofovir vs tenofovir alone; Phase II**
Sponsor	Hepatera Ltd.
Status	Ongoing
Source of Information	Trial registry[23] Journal article[24]
Location	Germany and Russia.
Design	Randomised, open-label, active-comparator.
Participants	N=120; aged 18-65 years; anti-HDV antibodies positive; serum HBsAg positive; positive PCR results for serum/plasma HDV RNA; Alanine transaminase level >1 x ULN, but less than 10 x ULN; Serum albumin >2.8 mg/dL; patients with liver cirrhosis or those without who failed prior interferon treatment.
Schedule	Randomised to; bulevirtide, 2 mg/day subcutaneously for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy; bulevirtide, 5 mg/day subcutaneously for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy; bulevirtide, 10 mg/day subcutaneously for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy; or tenofovir treatment for 48 weeks.
Follow-up	Active treatment for 48 wks, follow-up 12 wks.
Primary Outcomes	• HDV RNA negativation or decrease by ⩾2 log10 from baseline to Week 24 [Time frame: 24 weeks]
Secondary Outcomes	• Durability of HDV RNA response to 24 weeks post treatment [Time frame: 24 weeks] • Combined response: HDV RNA negativation or ⩾2 log decline and normal ALT at treatment week 24 [Time frame: 24 weeks] • Changes in ALT values at Week 24 and Week 48 compared to baseline [Time frame: 24 and 48 weeks] • Lack of fibrosis progression based on transient elastometry (Fibroscan) at Week 24 compared to baseline. [Time frame: 24 weeks] • Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 and Week 48 compared to baseline [Time frame: 24 and 48 weeks] • Changes in HBsAg (decreased levels, disappearance of HBsAg, antibodies to HBsAg) at Week 24 and Week 48 compared to baseline. [Time frame: 24 and 48 weeks] • Change in HBV DNA levels at Week 24 and Week 48 compared to baseline [Time frame: 24 and 48 weeks]
Key Results	• The primary endpoint was HDV RNA reduction by 2 log10 or negativity at the end of treatment and was achieved in 53.6%, 50.0%, 76.6% and 3.6% in the 2, 5 and 10mg bulevirtide cohorts and tenofovir alone cohort, respectively. • ALT normalization was achieved in 42.9%, 50%, 40% and 7.1%, respectively.

	• At follow up 12 week post-treatment, HDV RNA relapse occurred in 60%, 80% and 83% of treatment responder patients in the bulevirtide arms, respectively.
Adverse effects (AEs)	• Bulevirtide was very well tolerated. Apart from bile acids increase, no specific AE pattern could be identified for bulevirtide.
Expected reporting date	Study reported January 2018.

ESTIMATED COST

The cost of bulevirtide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical guideline. Hepatitis B (chronic): diagnosis and management (CG165). June 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- American Association for the Study of Liver Diseases. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. 2018.[25]
- European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. 2017[18]
- Turkish Association for the Study of the Liver. Diagnosis, management and treatment of hepatitis delta virus infection: Turkey 2017 Clinical Practice Guidelines. 2017[26]

ADDITIONAL INFORMATION

MYR GmbH did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Clinicaltrials.gov. *Phase 3 Study of Bulevirtide in Patients With CHD. Trial ID: NCT03852719*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03852719 [Accessed 11 December 2019].

2 European Medicines Agency. *EU/3/15/1500*. 2015. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3151500 [Accessed 11 December 2019].

3 MYR Pharmaceuticals. *Bulevirtide (Myrcludex)*. 2019. Available from: http://myr-pharma.com/science/about-myrcludex-b [Accessed 11 December 2019].

4 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *Journal of Hepatology*. 2012;57(1):167-85. Available from: https://www.sciencedirect.com/science/article/pii/S0168827812001675?via%3Dihub).

5 Bogomolov P, Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. *Journal of Hepatology*. 2016. Available from: http://www.sciencedirect.com/science/article/pii/S0168827816301489.

6 CISION. *MYR Pharma Announces Grant of Promising Innovative Medicine (PIM) Designation by British MHRA for Bulevirtide (Myrcludex), the First-in-Class Entry Inhibitor for Treatment of Chronic Hepatitis D Infections*. 2019. Available from: https://www.prnewswire.com/news-releases/myr-pharma-announces-grant-of-promising-innovative-medicine-pim-designation-by-british-mhra-for-bulevirtide-myrcludex-the-first-in-class-entry-inhibitor-for-treatment-of-chronic-hepatitis-d-infections-300806926.html [Accessed 11 December 2019].

7 European Medicines Agency. *PRIME: priority medicines*. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines [Accessed 11 December 2019].

8 MYR Pharmaceuticals. *MYR Pharma Announces Grant Of Breakthrough Therapy Designation By US FDA For Myrcludex, The First-In-Class Entry Inhibitor For Treatment Of Chronic Hepatitis B And D Infections*. 2018. Available from: http://myr-pharma.com/myr-pharma-announces-grant-breakthrough-therapy-designation-us-fda-myrcludex-first-class-entry [Accessed 11 December 2019].

9 Farci P, Anna Niro G. Current and Future Management of Chronic Hepatitis D. *Gastroenterology & hepatology*. 2018. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30166948.

10 Negro F. Hepatitis D virus coinfection and superinfection. *Cold Spring Harbor perspectives in medicine*. 2014;4(11):a021550-a. Available from: https://doi.org/10.1101/cshperspect.a021550.

11 World Health Organisation. *Hepatitis D*. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-d [Accessed 11 December 2019].

12 Healthline. *Decompensated Liver Disease*. 2018. Available from: https://www.healthline.com/health/decompensated-liver-disease [Accessed 16 December 2019].

13 Healthline. *Hepatitis D*. 2018. Available from: https://www.healthline.com/health/delta-agent-hepatitis-d [Accessed 11 December 2019].

14 National Health Service. *Hepatitis*. 2019. Available from: https://www.nhs.uk/conditions/hepatitis/ [Accessed 11 December 2019].

15 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

16 Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut*. 2000;46(3):420. Available from: https://doi.org/10.1136/gut.46.3.420.

17 National institute for Health and Care Excellence. *Hepatitis B (chronic): diagnosis and management (CG165)*. Last Update Date: October 2017. Available from: https://pathways.nice.org.uk/pathways/hepatitis-b-chronic/antiviral-treatment-in-adults-with-chronic-hepatitis-b#content=view-node:nodes-treatment-options-for-hepatitis-c-or-hepatitis-d-co-infection [Accessed 16 December 2019].

18 European Association for the Study of the Liver. *EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infectionq* Last Update Date: Available from: https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf [Accessed 12 December 2019].

19 EU Clinical Trials Register. *A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta. Trial ID: 2019-001213-17*. 2019. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001213-17/DE [Accessed 11 Decmeber 2019].

20 Clinicaltrials.gov. *Phase 2b Study of Bulevirtide (With Peginterferon Alfa-2a) in Patients With CHD. Trial ID: NCT03852433*. 2019. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03852433 [Accessed 11 December 2019].

21 EU Clinical Trials Register. *A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta. Trial ID: 2019-001485-15*. 2019. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001485-15/FR [Accessed 11 December 2019].

22 Clinicaltrials.gov. *Myrcludex B in Combination With Peginterferon Alfa-2a Versus Peginterferon Alfa-2a Alone in Patients With Chronic Viral Hepatitis B With Delta-agent. Trial ID: NCT02888106*. 2016. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02888106?term=NCT02888106&draw=2&rank=1 [Accessed 12 December 2019].

23 Clinicaltrials.gov. *A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination With Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients With Chronic Hepatitis D. Trial ID: NCT03546621*. 2018. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03546621 [Accessed 11 December 2019].

24 Gilman C, Heller T, Koh C. Chronic hepatitis delta: A state-of-the-art review and new therapies. *World journal of gastroenterology*. 2019. Available from: https://doi.org/10.3748/wjg.v25.i32.4580.

25 American Association for the Study of Liver Diseases. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *HEPATOLOGY*. 2018;67(4). Available from: https://www.aasld.org/sites/default/files/2019-06/HBVGuidance_Terrault_et_al-2018-Hepatology.pdf.

26 Yurdaydin C TF, Kaymakoglu S, Akarsu M, Akinci EG, Akkiz H et al. Diagnosis,management and treatment of hepatitis delta virus infection: Turkey 2017 Clinical Practice Guidelines. *Turk J Gastroenterol*. 2017. Available from: https://doi.org/10.5152/tjg.2017.20.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.