National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Bulevirtide for treating chronic hepatitis D [ID3732]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Association for the Study of the Liver (BASL) & British Society of Gastroenterology (BSG)	Yes-Hepatitis D has few effective treatment options and any advances in this field will be very welcome.	Thank you for your comment. No action needed.
	Hepatitis B Foundation UK	Yes. We have urgently awaited a treatment for hdv population since its discovery that offers real chances to seroconvert the virus.	Thank you for your comment. No action needed.
	MYR GmbH	yes	Thank you for your comment. No action needed.

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	NHS England & Improvement	Yes, it is appropriate.	Thank you for your comment. No action needed.
Wording	BASL & BSG	Yes but I am unclear as to whether the marketing authorisation will include combination treatment with pegylated interferon.	Thank you for your comment. Bulevirtide received marketing authorisation in July 2020. No action needed.
	Hepatitis B Foundation UK	Partly. More could be stated about the numbers cured and the cost of failing to cure the tiny number of hospitals stats recorded does not define the unmet needs of perhaps 20 to 40,000 HDV patients in the UK and their expected morbidity and mortality costs.	Thank you for your comment. The background section provides a brief summary of the disease and treatment pathway. Further details can be given at the submission stage. No action needed.
	MYR GmbH	Please be aware that changes have been made regarding the wording in several sections. Draft remit/appraisal objective: To appraise the clinical and cost effectiveness of Bulevirtide within its conditional marketing authorisation for treating chronic hepatitis D in adult patients with compensated liver disease.	Thank you for your comment. Bulevirtide will be appraised within its marketing authorisation. No action needed.

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	NHS England & Improvement	Yes.	Thank you for your comment. No action needed.
Timing Issues	BASL & BSG	In view of the lack of therapeutic options for hepatitis D this should be prioritised.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed.
	Hepatitis B Foundation UK	The urgency is high… no viral hepatitis is as good at killing quickly… awaiting diagnostic symptoms often means very expensive transplants resections or deaths. https://academic.oup.com/gastro/article/7/4/231/5522133	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed.
	MYR GmbH	Hepcludex is now approved in the European Union (EC decision 31.07.2020) therefore the company seeks a NICE appraisal in a timely manner in order to enable the treatment of patients with high medical need. Preparations are underway to be able to submit to NICE and we anticipate to be ready to submit by late January.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed.
	NHS England & Improvement	There are no current effective treatments for Hep D so it would be desirable to have the final guidance as soon as possible.	Thank you for your comment. NICE has scheduled this topic into its work programme. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BASL & BSG	The HES data suggest only 39 bed days - I am not sure how accurate this is likely to be. We have performed a liver transplant on a patient in the last 12 months for Hepatitis D which would contribute. Would be helpful to provide transplant and mortality data.	Thank you for your comments. The background section provides a brief summary of the disease and treatment pathway. Further details can be given at the submission stage. However, we have removed the number of beds from the background as suggested.
	Hepatitis B Foundation UK	The background overlooks that the bulk of chronic Hepatitis B and D is child acquired and this leads to **vast numbers in the UK being asymptomatic or unaware of their infections and risks of infection**. We feel the background to the approval of this new drug must include the BME and migrant communities endemic for HBV and that they are clear targets for its application if co infected with HBV and HDV. To date large numbers are unaware who is at risk of and infected with HBV and HDV due to a sex and drugs acquired incidence reportage unbalanced by the fact that thousands (the bulk) of those diagnosed are migrants and birthing mums with chronic childhood infections.	Thank you for your comments. The background section provides a brief summary of the disease and treatment pathway. Further details can be given at the submission stage. However, we have added more information about HBV/HDV testing and prevalence.

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		We also feel that the background could balance the Sentinel Surveillance figures for HBV and therefore HDV possible levels with the Hospital Episode Statistics. Sentinel Surveillance noted 2% were HBV infected in 2012 in London dropping to 1.3% in 2016 see **figure 7** https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/801174/London_hepatitis_B_report_2016.pdf point being an endemic capital is rather more motivating than 21 hospital admissions nationally in a backgrounding. Moving on a background study showing == In the years 2000–2006 in South London, the prevalence of anti-HD in ~1000 carriers of the HBsAg with chronic liver disease was 8.5% (Cross et al. 2008) also helps.	
	MYR GmbH	Chronic HDV infection represents the most severe form of viral hepatitis for millions of patients worldwide (Wedemeyer 2010). Hepatitis delta is liver inflammation caused by infection with the highly pathogenic Hepatitis delta virus (HDV) leading to acute and chronic liver disease. As HDV dissemination and replication strictly depends on the viral surface proteins of Hepatitis B virus (HBV), HDV prevalence is related to HBV prevalence. Of the worldwide approximately 257 million chronic HBV carries, 15-25 million subjects are estimated with be infected with HDV (Farci 2003, Wedemeyer 2010). However, the prevalence of HDV in the EU is below the Orphan Drug designation threshold. Calculation performed by the company estimates the prevalence of the chronically HDV infected patients in the EU to be in the range of 6,909 to maximum 20,492 subjects.	Thank you for your comments. The background section provides a brief summary of the disease and treatment pathway. Further details can be given at the submission stage. However, we have added more information about

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		The Hospital Episode Statistics for England 2018/19 recorded 21 admissions, 26 finished consultant episodes and 39 bed days for primary diagnosis of chronic viral hepatitis B with D virus infection (ICD-10 code B18.0). Acute HDV infection occurs as either co-infection or super-infection with HBV. HBV/HDV co-infection results in acute infection and clearance of both viruses in >90-95% of patients. HBV/HDV co-infection may course a more severe acute hepatitis compared to HBV monoinfection and is associated with increased risk of fulminant hepatitis (Rizzetto 2009). Super-infection of an HBsAg carrier can lead in 70-90% to CHD. Chronic HDV infections are characterized by persistently high levels of serum ALT and AST and high HDV viremia along with high titers of anti-HDV antibodies and usually a suppressed HBV replication (Farci et al. 2012). Chronic HBV/HDV infection represents the most severe form of viral hepatitis that rapidly progresses with increased risks towards liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (Rizzetto 2009, Wedemeyer et al. 2010). The liver disease associated with HDV runs a more progressive course than chronic hepatitis B (CHB) and may lead to cirrhosis within 2 years in 10–15% of patients (Yurdaydin et al. 2010). If left untreated, chronic HDV infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation (Niro et al. 2010, Buti et al. 2011, Heidrich et al. 2013). Liver cirrhosis and cancer occur 10-15 years earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV monoinfection (Cornberg et al. 2007). Chronic HDV infection causes cirrhosis and HCC with annual rates of 4% and 2.7%, respectively (Romeo et al. 2009, Gordien 2015). In the EU, no antiviral drug has been approved for the treatment of HDV until July 2020 when HEPCLUDEX was approved for the treatment chronic	HBV/HDV testing and prevalence.

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		hepatitis delta. Pegylated interferon alfa (PEG-IFNα) was used as a de facto treatment standard based on a very limited number of clinical studies. Current clinical experience indicates that ~50% of patients are eligible for interferon treatment due to contraindications, intolerabilities or advanced liver disease (Roulot et al. 2020, Kamal et al 2020). 25% thereof achieve a response; ~50% of these patient's relapse (Heidrich et al 2014). In fact, interferon therapy is only helpful for around 10% of patients and is not approved for HDV infection treatment. Clinical guidance 165, recommends a 48-week course of peginterferon alfa-2a for people co-infected with chronic hepatitis B and hepatitis D infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3). The aim of treatment is to prevent transmission and viral replication as well as the progression to cirrhosis, decompensation, hepatocellular carcinoma and liver failure.	
	NHS England & Improvement	Background information is complete.	Thank you for your comment. Please note, we have added more information about HBV/HDV testing and prevalence.
The technology/ intervention	BASL & BSG	Yes, frequency of administration should be included and whether combination therapy needs to addressed.	Thank you for your comment. Bulevirtide will be appraised within its marketing

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			authorisation. No action needed.
	Hepatitis B Foundation UK	**We need to settle a pathway/prescription plan for this drug that is most effective.** If Bulevirtide is giving 20% cure rate when combined with interferon alpha over 2 years, then we need to simply give it to all HBV HDV co infects as a matter of course. With the caveat that some may need a rest from interferon monotherapy prior to commencement or some maybe contraindicated as they react awfully to interferon. We need to describe what format is getting the best results from Bulevirtide and prescribe accordingly.	Thank you for your comment. Bulevirtide will be appraised within its marketing authorisation. No action needed.
	MYR GmbH	Bulevirtide (HEPCLUDEX®) is the lead compound of MYR GmbH, a German biotech company focusing of the treatment of chronic hepatitis B and D. The MYR GmbH is the conditional marketing authorization holder and market HEPCLUDEX® within the European Union and in the United Kingdom. The European commission approval was granted on 31th of July 2020. From August/September 2020 Bulevirtide is available for prescription in the European Union including UK. Bulevirtide has been designated as an orphan medicinal product (EU/3/15/1500), is a PRIME-designated product (EMA/PRIME/17/018) and is intended for the treatment of chronic hepatitis delta virus (HDV) infection in adult patients with compensated liver disease. (PIM granted on 18.12.2018) Bulevirtide is the first HBV/HDV entry inhibitor that binds and blocks the jointly used receptor sodium taurocholate co-transporting polypeptide (NTCP) on liver cells. Bulevirtide is a 47-amino acid synthetic peptide and was derived from HBV envelope protein. By blocking the hepatocyte surface protein (sodium	Thank you for your comments. The technology section was updated as suggested.

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		taurocholate co-transporting polypeptide [NTCP]), it misdirects HBV and co-infecting HDV to an unproductive pathway and prevents an infection of the cell. Bulevirtide is intended for the treatment regimen of patients with CHD as a subcutaneous injection of 2 mg Bulevirtide per day. The drug product is a lyophilized powder for injection that is supplied in single-use vials for reconstitution with 1 ml of sterile water for injection. The active ingredient is Bulevirtide acetate. Bulevirtide has been studied in five clinical trials with or without pegylated interferon alfa or nucleotide analogue therapy in adult patients with chronic hepatitis D and compensated liver disease. Clinical data on efficacy and safety of two phase II trials are the basis for the CMA. Currently, one randomized, multicentre phase III trial investigating the therapy regimen with Bulevirtide and one multicentre phase II trial study the treatment regimen with Bulevirtide and PEG-IFN are ongoing. Intervention(s): HEPCLUDEX® (INN: Bulevirtide)	
	NHS England & Improvement	Yes.	Thank you for your comment. No action needed.
Population	BASL & BSG	Yes-are there specific Hepatitis D genotypes likely to be suitable compared to others?	Thank you for your comment. If evidence allows, subgroups by disease severity will be considered.

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	Hepatitis B Foundation UK	**No**. Our HDV population needs to be tested far more comprehensively so we understand where it is. Yes WHO state a 5% of HBV patients have HDV but many studies have found high prevalences communities and nationalities. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4484953/ **We need to test and know if our Pakistani origin and Rumanian origin or African origin communities harbour pockets of plus 10% levels of co infection**. **Further if genotypes affect death rates and cure rates** https://academic.oup.com/gastro/article/7/4/231/5522133 Regarding the population and the amount of HBV patients accessing a HDV test and the barriers to accessing a HDV test the study https://pubmed.ncbi.nlm.nih.gov/25866333/ found **only 40% of HBV patients obtain a HDV test** during the 2002 2015 period. Since then on our helpline and social media interactions we note that the majority of HBV patients are quite unaware of their HDV status.	Thank you for your comments. The committee are unlikely to be able to make specific recommendations about the approaches to testing specifically but the issues regarding access to HDV testing can be highlighted by stakeholders in their evidence submission.
	MYR GmbH	Bulevirtide is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.	Thank you for your comment. If evidence allows, subgroups by disease severity will be considered.
	NHS England & Improvement	The population is difficult to predict but best estimates is less than 100.	Thank you for your comment. During scoping, variable estimates have been

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			provided on the number of people eligible to have this treatment were it to be recommended in a NICE appraisal. Stakeholders can make clear in their evidence submissions the most up to date information on potential eligible population. No action needed.
Comparators	BASL & BSG	Should not pegylated interferon be a comparator?	Thank you for your comment. Pegylated interferon was added to the list of comparators.
	Hepatitis B Foundation UK	Interferon and lifestyle advice is all we offer the co infected to date and Bulevirtide compares excellently against it. The lifestyle advice can continue alongside it as it has such vast importance in value.	Thank you for your comment. Pegylated interferon was added to the list of comparators.
	MYR GmbH	Best supportive care for the underlying HBV infection. As no drug, except Bulevirtide, is approved for the therapy of CHD, no best supportive care for a chronic HDV infection is available.	Thank you for your comment. Pegylated interferon was added to the list of comparators because it is currently used in the NHS for HDV infection.

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	NHS England & Improvement	Yes – BSC would be no treatment.	Thank you for your comment. Pegylated interferon was added to the list of comparators because it is currently used in the NHS for HDV infection.
Outcomes	BASL & BSG	Sustained virological response should be defined in terms of duration and durability. Are there plans to look at predictors of response in terms of viral kinetics (a less than 2 log drop had a 95% negative predictive value for virological response. Adverse events should specifically include bile acid elevations reported as a potential problematic side-effect.	Thank you for your comments. We have added virological and biochemical response to the list of outcomes.
	Hepatitis B Foundation UK	A real focus on clearance and functional cure numbers could be highlighted more.	Thank you for your comments. We have added virological and biochemical response to the list of outcomes.
	MYR GmbH	The outcome measures to be considered include: • ~~Sustained virologal response~~ The company considers the sustained virological response (SVR) as a non-relevant endpoint, as this virological endpoint for chronic HDV infection cannot be meaningfully applied as this is highly discussed. Undetectable HDV RNA at week 24 post-treatment was explored as secondary endpoint in some clinical studies, with the expectation that it might be associated with sustained	Thank you for your comments. We have updated the outcome from 'sustained virological response' to 'sustained response'. Development of resistance is a standard

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		virological response. However, long-term follow up studies such as the HIDIT-1 study revealed that more than 50% of patients with undetectable HDV RNA at 24 weeks post-treatment relapsed and developed detectable HDV RNA at least once during the follow-up (Heidrich et al. 2014), suggesting that some form of HDV latency exists in patients. Therefore, the company believes that no precise statement on the success of therapy or cure can be given based on the SVR, as CHD patients may demonstrate high relapse rates in the further course of the disease. We therefore propose to include the outcome morbidity: virological and biochemical response for the appraisal. ~~• development of resistance to treatment~~ Resistance development against a drug compound targeting a host protein is highly unlikely. As Bulevirtide targets the HBV entry receptor it is assumed that the resistance development, if possible, at all, will need a mutation within the HBV envelope protein. A selection for mutated subspecies needs active HBV replication. In practical terms, HBV replication in HDV co-infected patients will be either suppressed by HDV itself (Wu et al. 1995, Jardi et al. 2001, Heidrich et al. 2013), or by nucleoside/tide analog treatment in accordance with relevant guidelines. During both phase II trials, only three virological breakthroughs occurred during the program, whereas no evidence of resistance was demonstrated. Importantly, virological breakthroughs were even more common under interferon. In general, the development of resistance is very unlikely with Bulevirtide for several reasons: (i) targeting of a host protein, (ii) the necessity for mutations in HBV, whereas HBV replication can be efficiently controlled by nucleoside/nucleotide analogues,(iii) the highly conserved NTCP binding domain within the HBV preS1 domain and (iv) the fact that mutations within	outcome used in other technology appraisals of treatments for hepatitis infections. However, we have added virological and biochemical response to the list of outcomes.

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		this domain renders HBV/HDV non-infectious. Thus, the company believes that the respective outcome will not add any meaningful value. • morbidity: virological and biochemical response Instead the company suggests to add the outcome morbidity defined as a virological and biochemical response. As these outcome measures are acknowledged surrogate endpoints for the therapy of CHD patients. Both outcomes are considered to be beneficial. • mortality • adverse effects of treatment • health-related quality of life	
	NHS England & Improvement	Yes.	Thank you for your comment. No action needed.
Economic analysis	BASL & BSG	Everyone who has Hepatitis B in the UK should already be tested for Hepatitis D.	Thank you for your comment. No action needed.
	Hepatitis B Foundation UK	A step change study in cost effectiveness that includes the value of mass screening those in high infection level communities could be drawn on to help see https://bmjopen.bmj.com/content/9/6/e030183 a key aspect of this study is it overturns previous warped notions that migrant communities are not remaining endemic for the HBV they have migrated from, further it admits that HBV prevalence may well have tripled as sentinel surveillance figures for ante natal HBV levels have suggested during the 2000 to 2020 period. See https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/746267/hpr3618_bbv-ss.pdf **Other / Black / Asian groups test 3% HBV positive**	Thank you for your comments. No action needed.

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	MYR GmbH	One sentence was adapted: The use of Bulevirtide is conditional on the presence of HDV. The economic modelling should include the costs associated with diagnostic testing for HDV in people with hepatitis B. ~~who would not otherwise have been tested.~~	Thank you for your comment. This is standard wording. No action needed.
	NHS England & Improvement	No comments	-
Equality and Diversity	BASL & BSG	No changes required.	Thank you for your comment. No action needed.
	Hepatitis B Foundation UK	We dealt recently with an Essex child excluded from school for the entire calendar year from sept 1918 to sept 2019. He is now only allowed in school if he wears a long sleeve dress and avoids the kitchens and uses his special toilet, with constant one to one surveillance, even if he injures himself his mum is called to supply plasters or call an ambulance. He is BME and disabled. Discrimination of HBV is serious! We feel the advent of a step change cure opportunity for HBV and HDV could truly start to change this landscape. However if in expediting this medicine we do not also expedite testing for HBV and HDV, expedite our knowledge of which communities are afflicted and how they are afflicted in tandem we will be failing in our efforts for equality. There are processes that for 16 years we have found need to be borne in mind when asking people to come forward for testing for HBV/HDV.	Thank you for your comments. We have included your concerns in our Equality impact assessment form for this topic. Equality and Diversity issues will be discussed during the appraisal.

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		1. There is a powerful ongoing lobby that present HBV/HDV with a strong sex or drugs cause it focus. This drives away and underground the bulk of people at risk of HBV/HDV. 2. There is still a vast array of places that the statement “HBV is a 100 times as infectious as HIV” can be read on NHS websites. This causes almost limitless pain and shame and is quite sexually untrue and acts as a barrier to those at risk, or anyone thinking clearly. 3. Many patients are being culture and language barriers that need to be thought of when creating the new HBV/HDV lexicon. “Easy to manage when caught early, common child virus” is vastly more engaging and accurate to such groups. 4. There is often a residual fear of quarantine and deportation in the most infected groups and again this needs to be thought of when engaging them in testing and care. 5. With HCV new treatments we had a death reported from reactivated HBV, we noted that the FDA had a black box warning quicker than NICE on the issue. With these newer drugs affecting new areas of the species eg cccDNA, could we perhaps have an international radar for adverse events? Further with TAF we are seeing heart attack cholesterol issues and again are we moving fast enough at mandatory Lipid screenings for TAF users? 6. Large numbers of patients are poorly educated about side effects, the difference between chemotherapy side effects and peg interferon needs to be made clear. Many will ask “Ah that's the drug that makes you bald and infertile.” With a tenofovir plus bulveritide approach many will say “Ah that's the one that ruins your bones kidneys and embryos!”	

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	MYR GmbH	No changing needed. No equality issues anticipated.	Thank you for your comment. No action needed.
	NHS England & Improvement	Nothing identified.	Thank you for your comment. No action needed.
Other considerations	BASL & BSG	How this might fit in with current NICE guidance and in particular the oral antiviral and pegylated interferon treatments.	Thank you for your comments. Pegylated interferon was added to the list of comparators. Bulevirtide will be appraised within its marketing authorisation.
	Hepatitis B Foundation UK	Perhaps we need to study the big barrier to this medicine reaching the tens of thousands who need it. The lack of national awareness of Hep B and its causes and risk populations. During the year 1999 to 2000 WHO noted 20 million people were infected with HBV via reused medical syringes alone and this figure marches back annually through a lot of that century. See https://www.who.int/infection-prevention/publications/is_fact-sheet.pdf?ua=1 Millions and millions and millions of UK citizens in migrant communities and their onward generations are still unadvised of this catastrophe. Until we advise people of their exact risk they will not get tested. I am doing an Inquiry into infections of blood viruses from healthcare and after 60 million has been spent we are no nearer noticing that the main cause of hundreds of millions getting HBV was healthcare. “Ah you are from Pakistan/Uganda/Rumania where millions of unsterile medical injections helped HBV and infect more	Thank you for your comments. The committee may not be able to address these wider issues with regard to access to services and treatment specifically in a single technology appraisal however these can be raised in stakeholder submissions and be considered by the committee.

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		than half the child populations = get tested" Is simply not clear in our UK lexicon yet.	
	MYR GmbH	Not applicable.	Thank you for your comment. No action needed.
	NHS England & Improvement	Consideration should be given to its use in combination with pegylated interferon as part of the assessment.	Thank you for your comment. Bulevirtide will be appraised within its marketing authorisation.
Innovation	BASL & BSG	Yes, current therapies are poorly effective. Could the appraisal also consider liver transplant free survival/and or consider liver transplant costs.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.
	Hepatitis B Foundation UK	Yes this is a step change, we saw a boom in testing for HCV from thousands to 10's of thousands when ribavirin and interferon began to offer plus 20% cure rates in the early Noughties. Rolling this medicine could invigorate the entire areas of awareness and testing. Further cures are in the pipeline for HBV, as Professor Williams mentions in his Out of the Shadows Report, we could begin to out the shadows the whole Pandemic. The number one question we are asked daily on our platforms is when is a HBSAG and HDV sero negative opportunity / chance emerging. Many who know they have HBV but do not admit to their doctors may emerge, many	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.

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		who have fallen out of care may emerge, many who have never checked their status may emerge to. These benefits were very real with many ailments when news of functional curing became general.	
	MYR GmbH	The company considers Bulevirtide as being an innovative medicine with the potential to make a significant and substantial impact on the health-related benefits for CHD patients. As there has been no therapeutic regimen or drug until recently, Bulevirtide being approved as the first and only dedicated treatment for CHD patients demonstrated substantial antiviral efficacy as well as a good tolerability and safety profile.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.
	NHS England & Improvement	Yes – likely to supersede pegylated interferon as single agent of choice. Will be particularly useful in patients with decompensated HDV where pegylated interferon has poor outcomes.	Thank you for your comments. The extent to which the technology may be innovative will be considered during the appraisal.
Questions for consultation	Hepatitis B Foundation UK	Have all relevant comparators for bulevirtide been included in the scope? • How should best supportive care be defined? On this subject we tend to be good at defining care along the lines of tests to be done scans to be done and medicines or surgeries to be done. But the definition of 10 point counselling needed by each patient, the definition of patient education in liver care so they become expert in understanding their HBV panel, Liver Function and scan results and prognosis therefrom, the definition of what is a great liver friendly diet and	Thank you for your comments. Please note that access to testing is not the remit of this appraisal. Pegylated interferon was added to the list of comparators. Bulevirtide will be appraised within its marketing authorisation. We have added more

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		what is a dangerous liver harming diet. These areas need adding to our definition. With the bulk of patients still only under monitoring these things are the bulk of their care. How many people would you expect to be eligible for treatment with bulevirtide in the UK? Anywhere from 20 to 40,000, being 5 to 10% of HBV infections in the UK. Assuming UK HBV is about 400,000 people after the migration boom of arriving cases and the onward boom in our unvaccinated youth. See 8.7% of Somali children catching HBV horizontally by 5 see https://adc.bmj.com/content/86/1/67.3 and 1% of London children testing chronic in 2017 after 15 years of no vaccinations to endemic community children see Table 3 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/746267/hpr3618_bbv-ss.pdf What would you expect to be the treatment duration for people who would be eligible for bulevirtide? It seems the trials suggest 2 years. Is testing for hepatitis D virus antibody routine practice in the NHS for all people with chronic hepatitis B?	information about HBV/HDV testing and prevalence into the background section. Thank you for comment. No action needed.

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		Sadly it does not seem to be the case see https://pubmed.ncbi.nlm.nih.gov/25866333/ and there is a concern that more GP's are in charge of patients and a system wherein they non refer or part refer HBV patients is increasing. Are the outcomes listed appropriate? Are there any subgroups of people in whom bulevirtide is expected to be more clinically effective and cost effective or other groups that should be examined separately? To an extent those rapidly progressing to end stage liver disease will benefit most… the fat… the toxic… those with a family history of HCC…. Endemic communities may be more cost effective to test. Where do you consider bulevirtide will fit into the existing NICE pathway, hepatitis B (chronic)? Early Intervention for co infects prevents sudden onsets of extreme illness. • Would bulevirtide be used only after a prior treatment with pegylated interferon alpha-2a for hepatitis D, and for people in whom treatment with pegylated interferon alpha-2a is considered inappropriate? If so, how would people for whom pegylated interferon alpha-2a is not appropriate be defined?	Thank you for your comment. Severity of disease has been added to the final scope as a subgroup for consideration. Thank you for your comment. No action needed.

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		• Would bulevirtide be used alongside nucleoside/nucleotide analogue therapy for hepatitis B or would bulevirtide be used alone? • Would a combination with pegylated interferon alpha-2a be a treatment option for some people? If so, please explain who would be given a combination treatment with pegylated interferon alpha-2a? • How do prior treatments for hepatitis B influence the treatment pathway for hepatitis D? I feel the cold results of the clinical trials should inform these decisions…. Our excellent Liver Specialists have no doubt used this medicine and KPI ed which combo is best for who. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.	Thank you for your comment. No action needed.

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		Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. During the Infected Blood Inquiry some 2500 patient experiences have been defined all statements included an answer to the question of side effects from Interferon usage. I feel that lessons are there to be learnt about mitigating and managing these from these patient statements. The statements are held by Judge Langstaff as evidence so I do not understand the protocols for accessing them. Perhaps an approach could be made? But it would be remiss of me to have been involved in compiling such a list of 1500 plus interferon lessons and yet not mention it here as a body of work relevant to this appraisal . Do you consider bulevirtide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, it is a completely new era if we are dealing with offering a sero negative opportunity that can only improve in time. I can think of no motor to increase all aspects of HBV and HBV HDV coinfection awareness and testing and treating. Do you consider that the use of bulevirtide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	Thank you for your comments. No action needed. Thank you for your comments. The company and other stakeholder submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Perhaps we need to study the big barrier to this medicine reaching the tens of thousands who need it. The lack of national awareness of Hep B and its causes and risk populations. During the year 1999 to 2000 WHO noted 20 million people were infected with HBV via reused medical syringes alone and this figure marches back annually through that century. See https://www.who.int/infection-prevention/publications/is_fact-sheet.pdf?ua=1 Millions and millions and millions of UK citizens in migrant communities and their onward generations are still unadvised of this catastrophe. Until we advise people of their exact risk they will not get tested. I am doing an Inquiry into infections of blood viruses from healthcare and after 60 million has been spent we are no nearer noticing that the main cause of hundreds of millions getting HBV was healthcare. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).	calculation during assessment.
	MYR GmbH	**Have all relevant comparators for Bulevirtide been included in the scope?** • **How should best supportive care be defined?**	Thank you for your comments. We have added more information about HBV/HDV testing

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		All relevant comparators for Bulevirtide with respect to the underlying HBV infection have been considered for the scope, including PEG-IFN and NUCs. As no drug, except Bulevirtide, is approved for the therapy of CHD, no best supportive care for a chronic HDV infection is available and could be considered for the appraisal. **How many people would you expect to be eligible for treatment with Bulevirtide in the UK?** Treatment will be eligible for patients with chronic HDV and compensated liver disease. In line with the ODD and OMAR the theoretical mean HDV patient pool is estimated to be around 5812. Of this population the diagnosed HDV patient pool is estimated to be around 2325 (40%) of which 1627 (70%) will be compensated and therefore in line with the indication and eligible for treatment (see illustration below). If all patients of the theoretical mean HDV patient pool will be diagnosed, it is calculated that the compensated HDV patient pool and therefore eligible for treatment will be 4068 (70%) (see illustration below). It is assumed that with increasing diagnosis rate the patient pool will also increase. **Note: illustration and references not included in the form – see MYR consultation comments for more information.** **What would you expect to be the treatment duration for people who would be eligible for Bulevirtide?** The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit. Consideration to discontinue the treatment should be given in case of sustained (6 months) HBsAg seroconversion or loss of virological and biochemical response.	and prevalence into the background section and updated the outcomes section.

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		Is testing for hepatitis D virus antibody routine practice in the NHS for all people with chronic hepatitis B? In general, routine diagnostic testing for anti-HDV antibodies should be implemented for all patients with chronic hepatitis B as well as for patients being positive for HBsAg/HBcAg as well as HBV DNA. According to personal communication of the company, common HDV testing is not implemented routinely in all health facilities. **Are the outcomes listed appropriate?** The outcomes listed are appropriate with the expectations of sustained virological response and development of resistance to treatment. As described above the company considers the sustained virological response (SVR) as a non-relevant endpoint, as this virological endpoint for chronic HDV infection cannot be meaningfully applied as this is highly discussed. Undetectable HDV RNA at week 24 post-treatment was explored as secondary endpoint in some clinical studies, with the expectation that it might be associated with sustained virological response. However, long-term follow up studies such as the HIDIT-1 study revealed that more than 50% of patients with undetectable HDV RNA at 24 weeks post-treatment relapsed and developed detectable HDV RNA at least once during the follow- up (Heidrich et al. 2014). The occurrence of viral relapse suggest that some form of HDV latency exists in patients where HDV RNA was transiently undetectable in blood. Therefore, the company believes that no precise statement on the success of therapy or cure can be given based on the SVR, as CHD patients may demonstrate high relapse rates in the further course of the disease. We therefore propose to include the outcome morbidity: virological and biochemical response for the appraisal. In this context virological response is defined as a more than 2 $\log_{10}$ reduction in serum HDV RNA or undetectable HDV RNA at the end of treatment. A decline of 2 logs or more logs of HDV	

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		RNA at the end of treatment was recently acknowledged and recommended as a surrogate marker for treatment efficacy in clinical trials. Researcher as well as clinicians have widely agreed upon this endpoint (Yurdaydin et al. 2018). Biochemical response is defined at normalization of serum alanine aminotransferase (ALT) levels, a liver enzyme indicating the damage of the liver. Decline in ALT levels is an established surrogate marker for impact on necroinflammation, and thereby clinical benefit in viral hepatitis (EMA parallel consultation meeting 2018 between EMA and company). Furthermore, that company would like to remove the outcome resistance development, as resistance development against a drug compound targeting a host protein is highly unlikely. The outcome resistance development to treatment originates from treatment regimens for HBV infections unlike HBV therapies targeting a viral protein required for viral replication, Bulevirtide targets the host protein NTCP used by HBV/HDV as entry receptor. Bulevirtide does not target any viral protein needed for viral replication and/or dissemination. This has been acknowledged and agreed upon by EMAs safety advisory group meeting (SAG meeting between EMA and company). It is assumed that the resistance development, if possible, at all, will need a mutation within the HBV envelope protein. A selection for mutated subspecies needs active HBV replication. In practical terms, HBV replication in HDV co-infected patients will be either suppressed by HDV itself (Wu et al. 1995, Jardi et al. 2001, Heidrich et al. 2013), or by nucleoside/tide analogue treatment in accordance with relevant guidelines. During both phase II trials, only three virological breakthroughs occurred during the program, whereas no evidence of resistance was demonstrated. Importantly, virological breakthroughs were even more common under	

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		interferon. In general, the development of resistance is very unlikely with Bulevirtide for several reasons: (i) targeting of a host protein, (ii) the necessity for mutations in HBV, whereas HBV replication can be efficiently controlled by nucleoside/nucleotide analogues,(iii) the highly conserved NTCP binding domain within the HBV preS1 domain and (iv) the fact that mutations within this domain renders HBV/HDV non-infectious. Thus, the company believes that the respective outcome will not add any meaningful value. **Are there any subgroups of people in whom Bulevirtide is expected to be more clinically effective and cost effective or other groups that should be examined separately?** There are currently no subgroups of patients in whom Bulevirtide is expected to be more clinical effective **Where do you consider Bulevirtide will fit into the existing NICE pathway, hepatitis B (chronic)?** • **Would Bulevirtide be used only after a prior treatment with pegylated interferon alpha-2a for hepatitis D, and for people in whom treatment with pegylated interferon alpha-2a is considered inappropriate? If so, how would people for whom pegylated interferon alpha-2a is not appropriate be defined?** Buleviritde is the first and only approved therapy for CHD patients. Bulevirtide can be prescribed to patients independently of a prior treatment with PEG-IFN. Within the clinical studies efficacy and safety results demonstrate comparable results between naïve, previously treated, non-responders and patients with contraindications.	Thank you for your comment. Severity of disease has been added to the final scope as a subgroup for consideration. Thank you for comments. No action needed.

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		PEG-IFN is a non-approved therapy for the treatment of CHD patients (for efficacy of PEG-IFN in HDV treatment please see background section). • **Would Bulevirtide be used alongside nucleoside/nucleotide analogue therapy for hepatitis B or would Bulevirtide be used alone?** Bulevirtide can be used alongside with NUC therapy for the underlying HBV infection if indicated according to the current treatment guidelines (EASL 2017, Terrault et al. 2018). Our clinical program demonstrated that Bulevirtide and NUC can be safely administered together in patients with CHD and treatment was well tolerated**.** • **Would a combination with pegylated interferon alpha-2a be a treatment option for some people? If so, please explain who would be given a combination treatment with pegylated interferon alpha-2a?** As approved be the European Commission and recommended by the CHMP Bulevirtide can be used for the treatment of adult patients with chronic HDV infection and compensated liver disease. Co-administration with PEG-IFN for treatment of the underlying chronic HBV infection lies in the discretion of the attending physician. Clinical data of our phase II program demonstrated that co-administration of Bulevirtide and PEG-IFN is well tolerated and safe. • **How do prior treatments for hepatitis B influence the treatment pathway for hepatitis D?** Until recently, no therapeutic regimen or drug was approved for the dedicated treatment of CHD. PEG-IFNα was used as a *de facto* treatment standard and was the only	Thank you for comments. No action needed. Thank you for comments. No action needed. Thank you for comments. No action needed.

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		available off-label therapeutic option recommended by treatment guidelines (EASL 2017). However, current clinical experience indicates that only ~50% of patients are eligible for interferon treatment. Approx. 25% thereof achieve a response; ~50% of these patient's relapse. In fact, interferon therapy is only helpful for around 10% of patients and the benefit-risk in chronic HDV infection is not established. In CHD patients with ongoing HBV DNA replication therapy with nucleos(t)ide analogue (NA) should be considered (EASL 2017, AASLD 2018). NAs approved for treatment of HBV infection show negligible antiviral effects on HDV since they neither affect HDV replication nor suppress HBsAg production (Wedemeyer et al. 2011), which was further confirmed by the company in its phase II program. Thus, prior treatment for HBV will not impact the treatment pathway for HDV. **Do you consider Bulevirtide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** The company considers Bulevirtide as being an innovative medicine with the potential to make a significant and substantial impact on the health-related benefits for CHD patients. As there has been no therapeutic regimen or drug until recently Bulevirtide being approved as the first and only dedicated treatment for CHD patients demonstrated substantial antiviral efficacy as well as a good tolerability and safety profile. **Do you consider that the use of Bulevirtide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**	Thank you for your comments. The company and other stakeholder submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY

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		We are in the process of analysing available data and colleting QALY data from our ongoing clinical program phase II and phase III trials. These data will become available in the near future and may be part of the upcoming submission. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** The following data will be available for the Appraisal Committee: Phase II data (MYR202 and MYR203). Interim data on week 24 from phase III and phase II data (MYR301 and MYR204; Nov/Dec. 2020). **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No barriers = no treatment option for HDV, high unmet medical need.	calculation during assessment. Thank you for your comments. No action needed.
	NHS England & Improvement	Implementation will be via the existing HCV ODNs if approved and this should be part of the guidance recommendation. Currently HCD testing is recommended but poorly implemented.	Thank you for your comments. We have added more information about HBV/HDV testing and prevalence into the background section.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None.