NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Bulevirtide for treating chronic hepatitis D

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using bulevirtide in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using bulevirtide in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 25 November 2022
- Second evaluation committee meeting: 14 December 2022
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Bulevirtide is not recommended, within its marketing authorisation, for treating chronic hepatitis D with compensated liver disease in adults.

1.2 This recommendation is not intended to affect treatment with bulevirtide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with hepatitis D also have hepatitis B. There are no licensed treatments specifically for hepatitis D but standard care usually involves treating symptoms and the hepatitis B. People with significant fibrosis (scarring) in their liver can be offered peginterferon alfa-2a (PEG-IFN) off label.

The company positioned bulevirtide for people with chronic hepatitis D who have tried PEG-IFN and the condition did not respond, or for people who cannot have it. It also positioned it only for people with a METAVIR stage of F2 or over (which means they have significant fibrosis). Testing for METAVIR stage involves a biopsy, which is invasive and may have side effects, and many people refuse it.

Clinical trial evidence shows bulevirtide is effective compared with standard care. But there are uncertainties around how long it works for. There are also uncertainties because some people in the trial did not have a METAVIR stage and some had a stage of F1 or F0. Because of the uncertainties in the clinical-effectiveness evidence and in the economic model, the cost-effectiveness estimates are also uncertain. They are also above what NICE normally considers an acceptable use of NHS resources, even if the severity of the condition and its effect on quality and length of life are taken into account.

So bulevirtide is not recommended.

2 Information about bulevirtide

Marketing authorisation indication

2.1 Bulevirtide (Hepcludex, Gilead) has a conditional marketing authorisation 'for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV RNA positive adult patients with compensated liver disease'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for bulevirtide.

Price

2.3 The list price of bulevirtide is currently confidential. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Gilead, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers.

The condition, treatment pathway and positioning

Hepatitis D disease burden

3.1 Hepatitis D is an infectious disease of the liver caused by the hepatitis delta virus (HDV). Around half of all people who acquire HDV will develop chronic hepatitis D, defined as an infection lasting longer than 6 months. Hepatitis D only affects people who are already infected with the hepatitis B virus (HBV), because HDV needs the hepatitis B surface antigen to complete its replication. The patient expert explained the significant impact co-infection with hepatitis B and D has on their physical and mental health. They emphasised that the extreme lethargy associated

with the condition affects their day-to-day functioning and ability to walk short distances. They also explained that changes to their lifestyle such as stopping smoking or eating healthily have had limited impact on improving the symptoms of their condition, which have been a constant burden for over 10 years. The committee noted the high disease burden of chronic hepatitis D.

Treatment pathway and unmet need

3.2 The treatment options for people with chronic hepatitis D are limited. Clinical experts explained that people with hepatitis D would have treatment according to the recommendations in NICE's guideline on diagnosing and managing chronic hepatitis B. People co-infected with hepatitis D, with evidence of significant fibrosis, can be offered a 48-week course of peginterferon alfa-2a (PEG-IFN). Clinical experts explained that using PEG-IFN to treat hepatitis D is off label, can have serious side-effects, and is not effective for most people. They also said that a large proportion of people would also have antivirals (tenofovir and entecavir) for their underlying hepatitis B infection. If hepatitis B is cured, the hepatitis D virus cannot survive. But hepatitis B has a low chance of being cured with current treatments. Clinical experts explained that bulevirtide is a first-in-class medicine which addresses an unmet need for effective and well-tolerated treatments. They added that there is regional variation in providing tests for HDV, even though NICE's guideline on diagnosing and managing chronic hepatitis B recommends that everyone with HBV should have one. Clinical experts added that even if bulevirtide was available, there may still be reservoir of undiagnosed hepatitis D in those with undiagnosed hepatitis B. They also noted the limited number of laboratories testing for hepatitis D. However, if bulveritide was available, there would be an extra incentive to identify people with HDV, which may arguably make access to diagnosis more equal across the country. The committee concluded that there is a significant unmet need for effective treatments in this population because the current options are limited.

Positioning of bulevirtide in the treatment pathway

3.3 The clinical evidence presented for bulevirtide came from MYR 301, a phase 3, multicentre, open-label, randomised trial evaluating the clinical efficacy and safety of bulevirtide in people with chronic hepatitis D and compensated liver disease. The marketing authorisation also specifies that bulevirtide should be considered for people with chronic hepatitis D and compensated liver disease. The company positioned bulevirtide for a narrower population as a treatment for chronic hepatitis D with compensated liver disease and evidence of significant fibrosis, which it defines as a METAVIR fibrosis score of F2 or above. The condition should also have not responded well enough to PEG-IFN, or the person with hepatitis D should not be able to tolerate PEG-IFN or should have a contraindication. The company clarified that most people in MYR 301 had already had IFN treatment, and those who had not were likely to have a contraindication or not be able to tolerate it. The EAG accepted this but was concerned that the company's evidence included people not relevant to the decision problem it had specified. The company presented data from the full analysis set from MYR 301, which included people with all METAVIR fibrosis stages (F0 to F4), so it was unclear why the company positioned bulevirtide only for METAVIR stage F2 and above. The company explained that its positioning addressed the area of highest unmet need. The clinical experts said that everyone with hepatitis D has an unmet need for treatments that prevent disease progression, and if bulevirtide was recommended, they would prefer to use it as an alternative to PEG-IFN. The committee noted that it had not seen any effectiveness evidence compared with PEG-IFN so could not recommend bulevirtide in the wider population.

Fibrosis staging

3.4 The clinical experts explained that it would be difficult to identify the company's proposed population in clinical practice. METAVIR staging is done using a liver biopsy, which is invasive and carries a morbidity and mortality risk. Therefore, many people refuse this procedure. The

committee agreed that, even if it accepted that it is clinically appropriate to limit bulevirtide to people with significant fibrosis, it may not be possible to implement such a rule in practice. NICE's guideline on diagnosing and managing chronic hepatitis B recommends a non-invasive assessment, transient elastography (FibroScan), for everyone with HBV. Liver biopsy is only offered to confirm the level of fibrosis in adults with a transient elastography score of between 6 kPa and 10 kPa. The clinical experts explained that, in practice, clinicians would likely use transient elastography to determine eligibility for bulevirtide, along with serological tests and imaging. The committee heard that the company had collected transient elastography data in MYR 301. It concluded that, if it was not possible to position bulevirtide as a first-line treatment, it would be useful for the company to present data using transient elastography rather than liver biopsy (METAVIR staging) to assess fibrosis. This is because this approach more closely reflects current clinical practice for determining fibrosis stage to identify eligible people.

Clinical effectiveness

Virological and biochemical response

3.5 The MYR 301 trial compared 2 different doses of bulevirtide (2 mg and 10 mg) with 48-week delayed treatment with bulevirtide 10 mg (that is, people had standard care until 48 weeks, at which point they started on bulevirtide), over 144 weeks. The company used 48-week data from the bulevirtide 2 mg arm and delayed treatment arm to reflect the intervention and comparator. The primary outcome of MYR 301 was combined virological and biochemical response at week 48. Virological response was defined as undetectable HDV RNA or a decrease in HDV RNA levels by $2\log_{10}$ IU/ml or more from baseline. Biochemical response was defined as alanine aminotransferase (ALT) normalisation, that is, ALT levels in the normal range. In the MYR 301 trial, many more people on bulevirtide had a combined response than people who had standard care at 24 weeks and 48 weeks of treatment. This difference was statistically significant. The committee noted that people in the delayed treatment arm of the trial

were allowed to continue with any treatment prescribed for their underlying hepatitis B. It agreed that this arm represented standard care in the UK. The committee acknowledged the large benefit for people who had treatment with bulevirtide at week 48, but noted that the 48-week treatment period in MYR 301 was quite short. It concluded that longer-term data would be useful to determine if response with bulevirtide is sustained into the longer term.

Surrogate outcomes

3.6 It is not feasible to assess long-term complications of hepatitis D, such as decompensated cirrhosis, hepatocellular carcinoma and death directly in clinical trials, as these may take years to develop. Because of this, surrogate outcomes are used. The clinical experts said the surrogate outcomes of virological and biochemical response used in MYR 301 were reasonable markers of disease progression in hepatitis D. However, they explained that some people's ALT levels may not normalise with treatment because of other reasons such as fatty liver disease or alcohol use, and using the combined endpoint may disadvantage those with raised ALT if treatment was stopped in these people. They added that undetectable HDV was also a good indication of treatment efficacy. The committee concluded that virological and biochemical response can be considered suitable surrogate outcomes for preventing the complications of liver disease.

Generalisability

3.7 Because MYR 301 did not include people in the UK, the company assumed that the baseline characteristics of people taking bulevirtide in the NHS would reflect the cohort reported by Spaan et al., a retrospective analysis of 107 people with hepatitis D in the UK. People in Spaan et al. had a baseline age of 35 years and 60% had cirrhosis. In MYR 301 the baseline age was 42 years and 47% had cirrhosis. The EAG said the baseline characteristics in Spaan et al. and MYR 301 were both clinically plausible, but the model was sensitive to these inputs in terms of the cost-

effectiveness results and the severity weighting applied. The company also presented data published by Public Health England (now the UK Health Security Agency [UKHSA]) on routine blood-borne virus testing. The median age between 2011 to 2020 was around 36 years. The committee noted that this data was provided after technical engagement stage, so could not be fully reviewed by the EAG. Further to this, one of the clinical experts explained that they are the lead investigator of a study being done by the UKHSA on the epidemiology of HDV infection in the UK. The study is collecting data from the 10 laboratories doing HDV testing in the UK and data should be available on mean age at baseline. The committee agreed with using UKHSA data, but considered that data on mean (rather than median) age and the proportion with cirrhosis on diagnosis would be helpful.

Economic model

Company's modelling approach

3.8 The company presented a Markov model to estimate the cost effectiveness of bulevirtide compared with standard care. The model had 10 health states, representing METAVIR fibrosis stages F0 to F4, and more severe disease complications including decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-liver transplant and death. The model had a 24-week cycle length and used a lifetime time horizon. Because the company positioned bulevirtide in people with METAVIR stage of F2 and above, the F0 to F1 states in the model were never occupied. The committee noted that using model health states based on METAVIR fibrosis staging, may not be appropriate (see sections 3.3 and 3.4). The committee considered that if the company were to amend its population and comparators to cover the entire marketing authorisation, then a model structure using METAVIR stages may be acceptable because data from the full trial population could be used. The committee concluded that if the company is planning on positioning in a narrower population than the marketing authorisation, an elastography-

based model (with effectiveness data from the relevant population alone) would be preferred.

Transition probabilities

3.9 Initial transition probabilities in the model were determined by response status in MYR 301. Although the company positioned bulevirtide for people with METAVIR stage F2 and above, it used data from the full trial population to estimate probabilities of response, which included people with METAVIR stage F0 to F1. The EAG noted that people with less severe fibrosis may be more likely to have a better response, which may overestimate response rates in population with METAVIR stage F2 and above. In the longer term, the company assumed that people with a combined response (from now referred to as combined responders) did not progress through fibrosis states or to more severe disease states, such as hepatocellular carcinoma, and could experience fibrosis regression from 24 weeks onwards. The company assumed an 8.8% annual probability of regression from F4 to F3, and a 13.3% annual probability of regression from F3 to F2. The company assumed that people with a virological response only (from now referred to as virological responders) could progress, albeit at a slower rate than people whose condition did not respond to treatment at all (from now referred to as non-responders). Clinical experts agreed with the company that combined responders would have a low risk of progression through fibrosis stages, but argued that this would not be zero because this group could still have detectable levels of virus. They added that even combined responders may still be at risk of hepatocellular carcinoma. Clinical experts further explained that it is plausible that fibrosis regression could occur in combined responders, but added that the company's assumed transition probabilities for fibrosis regression seemed high. The committee agreed with the clinical experts that combined responders would still be at risk of hepatocellular carcinoma, and noted that in people with hepatitis B and hepatitis C, viral response reduces, but does not eradicate hepatocellular carcinoma risk. The committee noted that the EAG assumed a residual

risk of hepatocellular carcinoma in its base case, so it preferred to align with the EAG's assumption on this. The committee concluded that additional scenario analyses may help to address the remaining uncertainties around transition probabilities (section 3.16).

Duration of response

3.10 The company's assessment of response was based on 48-week data from MYR 301, extrapolated for 1 additional model cycle to 72 weeks. The EAG preferred to limit the timeframe for assessing response to 48 weeks, without extrapolating data from MYR 301. It argued that the company's extrapolations are uncertain because they assume that response is maintained for all people who do not stop treatment from 48 weeks onwards. The committee considered the data on response at week 24 and 48 and noted that some people lost response, while others gained response. But the trend is likely to be for people to lose response over time as treatment is stopped for non-responders. The committee heard from the company that additional data from MYR 301, beyond 48 weeks, will soon be available. The committee concluded that additional trial data would be helpful in resolving the uncertainty around ongoing response and give the committee confidence in the response rates seen at 48 weeks. However, until this data is available, the committee agreed with the EAG that response should be limited to 48 weeks because this is aligned with the data currently available.

Treatment duration and stopping rules

3.11 The summary of product characteristics for bulevirtide says that treatment should be continued for as long as it is associated with a clinical benefit. The company assumed that treatment duration in the model depends on response status. Combined responders were assumed to remain on treatment indefinitely, whereas virological responders and non-responders stopped at 72 weeks and 48 weeks respectively. The EAG highlighted the mismatch between treatment duration in the model and in the trial: everyone in the trial could continue treatment, irrespective of response

status. Clinical experts broadly agreed with the company's model assumptions for combined responders and non-responders but were less sure of what would happen for virological responders. One clinical expert explained that if a patient had a virological response but high ALT for reasons other than hepatitis, for example fatty liver disease or alcohol use, clinicians would be wary about stopping treatment. Clinical experts added that treatment would also likely continue for combined or virological responders who develop hepatocellular carcinoma, and that for people with convincing evidence of virus eradication, treatment would likely be stopped. The committee agreed with the clinical experts' assumptions but noted that there is remaining uncertainty around whether the stopping rules assumed by the company are aligned with those used in MYR 301 until data beyond 48 weeks becomes available.

Utility gain for combined responders

3.12 The company applied a utility gain for combined responders to capture the benefit of having the combined outcome of virological and biochemical response. The committee noted that the utility gain for combined responders was a key driver of cost effectiveness. The company fit a Tobit regression model to 48-week pooled data from MYR 301. Variables included in the model, informed by clinical experts, were cirrhosis status at baseline and response at week 48. The utility gain was applied in addition to utility for the F2 to F4 health states for people with a combined response. The committee heard from clinical experts that it was plausible for people's symptoms and quality of life to improve with the reduction in viral load. It concluded that it was reasonable to assume a utility gain for combined responders. The committee was less certain about the size of the utility gain that should be applied. It noted the lack of justification for the Tobit approach and highlighted that the resulting utility gain from the regression model was not statistically significant. It recalled that in previous appraisals of hepatitis C, combined response was associated with a smaller utility gain than assumed by the company. The committee

concluded that the size of the utility benefit for combined responders was uncertain.

Health-state utility values

3.13 The MYR 301 trial collected EQ-5D-3L data at baseline, week 24 and week 48. The company argued that trial EQ-5D data did not demonstrate face validity because it did not reflect differences between people with and without compensated cirrhosis. It added that key symptoms of hepatitis such as fatigue, nausea and vomiting are not well reflected by EQ-5D-3L. The company could not identify appropriate utility values for people with chronic hepatitis D in the literature, so preferred to use utility values from a meta-analysis of people with chronic hepatitis B. The EAG disagreed with the company's view that utilities based on MYR 301 are not appropriate because the EAG's experts highlighted that the impact of different levels of fibrosis on quality of life is likely to be very small. The committee agreed with the EAG and noted that even histologically advanced liver disease is silent in many people and decompensation is often the presenting event. The committee concluded that utilities based on MYR 301 are appropriate.

Costs

3.14 Bulevirtide is available as a 2 mg powder for injection vial, reconstituted self-administered daily. According to the summary of product characteristics, people self-administering should get training to minimise the risk of injection site reactions. The company explained that it would fund all homecare services, including training to self-administer, so these costs are not included in the model. The committee concluded that the model includes all relevant costs associated with bulevirtide treatment.

Severity modifier

3.15 The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company calculated absolute and proportional quality-adjusted life year (QALY) shortfall weights in line

with NICE's health technology evaluations manual. Absolute QALY shortfall is the future health, including quality and length of life, that is lost by people living with a condition, compared with the expected future health without the condition over people's remaining lifetime. Proportional QALY shortfall represents the proportion of future health, including quality and length of life, that is lost by people living with the condition. The company estimated that a weight of 1.2 should apply. It used baseline characteristics based on Spaan et al. in its calculation of QALYs accrued by a healthy individual in the general population. Baseline age was 35 years and 59% were men. QALYs for people on standard care were taken from the comparator arm of the model. The EAG considered that the company had calculated the severity weighting appropriately but noted that the weighting was sensitive to the assumed age at baseline as well as the proportion with cirrhosis. The committee added that many of the EAG's preferred assumptions around the natural history modelling of chronic hepatitis D may also affect the severity weighting calculations because they affect QALYs accrued by people having standard care. The committee noted that it would like to see the mean age and cirrhosis status of UK patients at diagnosis based on UKHSA data. It added that validation of the model predictions for people on standard care using external literature sources would be helpful, along with graphical representations of health state occupation over time.

Committee's preferred assumptions

3.16 The committee considered the differences between the company's and the EAG's base case assumptions. The committee favoured the EAG's assumptions but noted that the baseline age in MYR 301 seemed higher than expected for people in UK clinical practice.

The committee noted concerns around the high level of uncertainty, specifically:

- the company's proposed positioning in people with METAVIR stage F2 and above (section 3.3 and section 3.4)
- the mean age of people diagnosed with hepatitis D in the UK (section 3.7)
- response rates beyond 48 weeks in MYR 301 (section 3.10)
- treatment duration beyond 48 weeks in MYR 301 (section 3.11)
- the size of the utility gain for combined responders (section 3.12)
- the long-term survival for people on standard care, in the absence of bulevirtide (section 3.15)

The committee would like to see the following scenario analyses:

- a low but not zero risk of progression through fibrosis stages for combined responders (section 3.9)
- a low but not zero risk of progression to hepatocellular carcinoma for combined responders (section 3.9)
- a lower probability of fibrosis regression for combined responders (section 3.9)
- treatment continued for people who develop hepatocellular carcinoma (section 3.11)
- the same treatment continuation assumptions for virological responders as combined responders (section 3.11)
- treatment stopped for those with convincing evidence of virus eradication (section 3.11)
- alternative estimates of utility gain for combined responders, based on previous hepatitis appraisals (section 3.12).

The committee would also like to see:

- transient elastography data, to ensure any recommendation made is implementable (section 3.4)
- mean age and proportion with cirrhosis on diagnosis for people in the UK with hepatitis D, based on UKHSA (section 3.7)

- if possible, the evolution of response diagram (evidence assessment report figure 2) with updated data beyond 48 weeks, to validate model predictions around ongoing response (section 3.10)
- further justification for selection of the Tobit model and variables included in the regression analysis (section 3.12)
- natural history of hepatitis D for people on standard care to validate model predictions (section 3.15)
- graphical representations of health state occupation over time from the economic model (section 3.15).

Cost-effectiveness estimates

3.17 The company's deterministic incremental cost-effectiveness ratio (ICER) for bulevirtide compared with standard care was £27,612 per QALY gained, including the commercial discount for bulevirtide and a 1.2 QALY weight (section 3.15). The EAG presented a range of ICERs using alternative assumptions. The highest ICER presented by the EAG was £48,097. This included the EAG's preferred assumptions, baseline characteristics based on MYR 301, and a QALY weight of 1. Probabilistic ICERs were slightly higher than deterministic ICERs. Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Other considerations

Innovative Medicines Fund

3.18 The committee recognised that bulevirtide is a promising treatment, but could not recommend it for routine commissioning because of the uncertainty in the clinical and cost-effectiveness estimates. It noted that bulevirtide may be eligible for the Innovative Medicines Fund (IMF). So the company is invited to submit a proposal NHS England for the IMF. The IMF criteria are:

- The intervention must be an innovative, non-oncological technology with clinical promise (that is, it provides significant clinical benefits to patients or represents a step change in medicine).
- The technology addresses a high unmet need.
- The technology is associated with significant uncertainty surrounding the cost effectiveness.
- The uncertainty can be addressed with further evidence generation in the next 2 to 3 years.

Uncaptured benefits

3.19 The committee also heard about several benefits of bulevirtide that were not captured by the QALY calculation. It noted the rarity of hepatitis D and that bulevirtide is the first licensed treatment in this area, addressing an unmet need, and is therefore innovative. Clinical experts pointed out that the treatment would reduce the viral load in infected people, prevent the spread of infection and reduce the stigma around this blood-borne virus. The committee noted that these benefits were not captured within the cost-effectiveness analysis, but the benefits were not enough to outweigh the committee's concerns around the degree of uncertainty around the ICER.

Equality issues

3.20 The committee noted that chronic hepatitis D disproportionately affects people from a Black African family background. It heard that migrant HDV infections are increasing and native HDV infections are decreasing because of HBV vaccination programmes. It accepted that bulevirtide would be a welcome option and could address these potential issues.

Conclusion

3.21 The committee concluded that it could not recommend bulevirtide for treating chronic hepatitis D in people with a METAVIR fibrosis stage of F2 or above. Testing for METAVIR status involves a biopsy, which is not routinely done for people with chronic hepatitis D in clinical practice. More

data is also needed before uncertainties in the clinical evidence and cost-effectiveness estimates can be resolved (section 3.16).

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Anna Willis

Technical lead

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