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Guideline on the clinical evaluation of medicinal products intended for the treatment of chronic hepatitis B (CHB)

Draft

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This guideline replaces the guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHMP/EWP/6172/03).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Chronic Hepatitis B (CHB), Hepatitis B virus (HBV), functional cure, finite treatment approaches, chronic suppressive treatment approaches

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Guideline on the clinical evaluation of medicinal products intended for the treatment of Hepatitis B (CHB)

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Executive summary

This is the first revision of the guideline on the clinical evaluation of medicinal products intended for the treatment of hepatitis B (CHMP/EWP/6172/03).

The main aim of this revision is to address clinical trial requirements including studies that aim to demonstrate the efficacy of novel treatments or combination treatment regimens for viral suppression, including chronic and finite treatment, and/or finite treatment for functional cure of chronic hepatitis B (CHB). Medicinal products intended for the prevention of hepatitis B infection and for treatment of acute hepatitis B are not covered.

In line with recent developments, the primary endpoints relevant for achieving viral suppression or functional cure have been updated. In addition, guidance is given on safety and efficacy considerations when stopping suppressive nucleosid(t)e (NUC) treatments in clinical trials that evaluate finite regimens and regimens intended to achieve functional cure. Furthermore, information on statistical analyses in trials that evaluate finite treatment regimens is included. The revision also addresses and/or updates specific considerations for agents with novel mechanisms of action, definitions of cure, diagnostic criteria and patient characteristics.

Introduction (background)

Human Hepatitis B Virus (HBV) is an enveloped DNA virus belonging to the *Hepadnavirus* family. In the host, the virus replicates and assembles exclusively in hepatocytes, and virions are released non-cytopathically through the cellular secretory pathway. The viral genome consists of the small (3.2 kb), partially double-stranded, relaxed-circular (rc) DNA, which has four open reading frames encoding 7 proteins: HBeAg (HBV envelope antigen, secreted dimeric protein), HBcAg (HBV core antigen, viral capsid protein), HBV Pol/RT (polymerase, reverse transcriptase activity), PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins), and HBx (HBV x antigen, regulator of transcription required for the initiation of infection). In the nucleoplasm, the rcDNA is converted into a covalently closed circular DNA (cccDNA), which functions as non-replicative minichromosome that persists throughout the lifespan of infected hepatocytes. Besides encoding the capsid protein and the viral polymerase, the pre-genomic RNA is reverse transcribed into new rcDNA within the viral capsid. The DNA containing nucleocapsids in the cytoplasm are either recycled into the nucleus to maintain the cccDNA reservoir or enveloped and secreted via the endoplasmic reticulum. Viral genome integration in the host genome can occur randomly but it is not required for viral replication. However, it is one of the important mechanisms involved in hepatocyte transformation.

Chronic hepatitis B (CHB) is a major cause of liver disease and cancer, affecting over 250 million people worldwide. CHB infection results in progressive liver disease ranging from asymptomatic to severe disease with complications including cirrhosis, decompensation, liver failure, and the development of hepatocellular carcinoma (HCC).

Effective vaccines and antiviral therapies are approved in the EU for prevention and treatment of CHB.

Current EU approved therapies include NUCs and pegylated interferon (pegINFa). These treatments can achieve sustained suppression of HBV DNA during continued treatment (NUCs) or finite treatment (pegINFa). Sustained HBV DNA suppression is associated with serum aminotransferase (ALT) normalisation and improvement in liver histology including regression of hepatic fibrosis and cirrhosis, so reducing the risk of hepatic decompensation, liver failure and HCC. However, the rates of HBsAg loss with or without detection of anti-HBsAg are low. Clearance of HBsAg is considered to be the best predictor of sustained remission off-treatment.

New treatment approaches include finite regimens aimed at sustained viral suppression and regimens aimed at functional cure, defined as sustained suppression of HBV DNA and sustained HBsAg loss with or without HBsAg seroconversion after treatment has been stopped.

1. Scope

This guideline is focussed on the clinical development of medicinal products for the treatment of CHB, including direct acting antiviral agents (DAAs) and immunomodulatory agents. Guidance is provided on the clinical development of novel treatments aimed at sustained viral suppression and/or functional cure, including finite and combination treatment regimens.

The development of medicinal products intended to prevent hepatitis B infection, to treat acute hepatitis B, to achieve sterilising cure and therapeutic vaccines is not covered in this guideline.

2. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and relevant EU and ICH guidelines. These include, but are not limited to:

- ICH E4 Dose-response information to support drug registration (CPMP/ICH/378/95)
- ICH E9 Guideline on statistical principles for clinical trials - Step 5 (CPMP/ICH/363/96)
- ICH E9 (R1) Step 5 Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017).
- ICH E10 Choice of a control group in clinical trials (CPMP/ICH/364/96)
- EMA guideline on the choice of the non-inferiority margins (EMEA/CPMP/EWP/2158/99)
- ICH E1A guideline on the extent of population exposure to assess clinical safety for drugs (CPMP/ICH/375/95)
- EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02)
- EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/725881/2015)
- EMA guideline on pharmacokinetic studies in man (CHMP/EWP/147013/04)
- EMA guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)
- EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/ Rev.1 Corr.2**)
- ICH M15 guideline on general principles for model-informed drug development – Step2b (EMA/CHMP/ICH/496426/2024)
- EMA guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016)
- EMA guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)

- Reflection paper on the pharmaceutical development of medicines for use in the older population (EMA/CHMP/QWP/292439/2017)
- ICH E6(R2) guideline on good clinical practice (EMA/CHMP/ICH/135/1995)
- EMA Guideline on data monitoring committees (EMEA/CHMP/EWP/5872/03 Corr)
- ICH E11 guideline on the clinical investigation of medicinal products in the paediatric population Step 5 (CPMP/ICH/2711/99)
- ICH E11(R1) addendum to the guideline on clinical investigation of medicinal products in the paediatric population - Revision 1 (addendum) (EMA/CPMP/ICH/2711/1999)
- ICH E11A guideline on paediatric extrapolation (EMA/CHMP/ICH/205218/2022)
- EMA guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (CHMP/EWP/147013/04)
- EMA guideline on the pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
- EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/1897724/2018).
- EMA guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02 Rev. 3)
- EMA guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)
- EMA guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005)

3. Patient selection

Initial clinical trials to evaluate safety and pharmacokinetics of DAAs and immunomodulators for CHB are expected to be conducted in healthy adults. Patients to be enrolled in clinical trials investigating treatments for CHB should fulfil established criteria for CHB infection.

Early clinical trials in patients with CHB should focus on adults without cirrhosis before proceeding to evaluate other populations. Depending on what is known about the safety and pharmacokinetics of the agent under evaluation, it may be appropriate to conduct trials that include patients with cirrhosis, patients with decompensated CHB, immunocompromised patients, paediatric patients and those who are co-infected with HIV-1 or HDV.

Trials of new treatments intended to achieve and maintain viral suppression may be conducted in viraemic patients who are treatment-naïve and/or in patients who have been previously treated but are off treatment and viraemic at study entry. Trials of new treatments intended to achieve functional cure will usually be conducted in patients who are virologically suppressed on NUC treatment but without loss of HBsAg or in viraemic patients who are treatment naïve or off-treatment.

It is recommended to conduct separate studies in HBeAg-positive and HBeAg-negative patients or, at least, to stratify based on HBeAg status, if not studying these in separate trials. Other stratification factors could include, but are not limited to, baseline HBV DNA levels, presence or absence of cirrhosis, baseline HBsAg levels and treatment history.

Generally, the inclusion and exclusion criteria should ensure that enrolment is limited to those patients eligible for anti-HBV therapy in line with current treatment guidelines. However, it may sometimes be justifiable to include an alternative study population that currently lacks a recommendation for treatment provided that available data indicate that the investigational product (IP) could be of clinical benefit in that population. As the clinical picture of CHB ranges from asymptomatic infection to symptomatic chronic hepatitis, liver cirrhosis, liver decompensation and HCC and may include immune-mediated extrahepatic manifestations, no specific symptoms are generally required for inclusion in CHB studies. benefit in that population. As the clinical picture of CHB ranges from asymptomatic infection to symptomatic chronic hepatitis, liver cirrhosis, liver decompensation and HCC and may include immune-mediated extrahepatic manifestations, no specific symptoms are generally required for inclusion in CHB studies.

The selection criteria should specify eligibility according to disease stage, duration of disease, disease activity (including virological, serological and biochemical parameters, absence or presence of cirrhosis), occurrence of complications and previous treatments. Considering the fluctuating course of HBV infection, some eligibility criteria (e.g. ALT, HBV DNA and HBeAg/anti-HBe) may take into account results recorded during routine care on more than one occasion over a 6-month period prior to study baseline.

4. Assessment of efficacy

The most appropriate primary efficacy endpoint and the timing of assessment of clinical efficacy in clinical studies may be different depending on the mechanism of action, the half-life of the drug, the treatment approach (e.g. chronic suppressive treatment, finite treatment, functional cure, combination therapy) and the intended patient population.

The treatment goals may differ and may include sustained HBV DNA suppression on- or off-treatment or functional cure off-treatment. Functional cure is defined by sustained suppression of HBV DNA and sustained HBsAg loss with or without anti-HBs seroconversion.

For clinical trials aimed at functional cure, it is expected that the candidate regimen will be discontinued after a pre-defined treatment duration. As stopping long-term NUC therapy by itself is known to significantly increase the HBsAg loss rates and thus functional cure in a subset of patients, specific considerations for stopping treatments, including baseline demographic and diseases characteristics that could impact the efficacy outcome are given in section 5.2.2.3

In principle, three primary endpoints can be accepted depending on the chosen treatment approach as described in section 5.2.2:

1. Sustained suppression of HBV DNA on treatment,
2. Sustained HBV DNA suppression after treatment cessation, and
3. A co-primary endpoint of sustained suppression of HBV DNA and sustained HBsAg loss with or without anti-HBs seroconversion after treatment cessation.

To assess consistency of the efficacy results, outcome-by-region and outcome by HBeAg status, if HBeAg-positive and HBeAg-negative patients are enrolled, should be evaluated.

The use of primary endpoints other than HBV DNA suppression and HBsAg loss, e.g. reductions in HBsAg levels from baseline or cccDNA clearance in confirmatory trial is not encouraged because these are at the time of writing this guideline not considered sufficiently validated and thus are currently regarded as exploratory endpoints. In addition, the lack of standardised, validated assays able to

evaluate e.g. cccDNA raise feasibility concerns. Sponsors proposing non-validated biomarkers as primary efficacy endpoint should discuss with EU Regulators early in clinical development.

The definition of a responder in terms of treatment response-based assessment of parameters that define the chosen primary efficacy endpoint should be pre-defined in the clinical study protocol. Also, virological failure should be clearly defined in the study protocol. Usually, virological failure is defined as a confirmed increase of ≥ $1\log_{10}$ HBV DNA copies/mL above nadir, quantifiable HBV DNA after being < LLOQ, or never achieved HBV DNA levels < LLOQ.

Long-term follow-up of clinical outcomes (i.e. after the primary endpoint has been determined) is required to ensure sustained clinical response whether the aim is viral suppression, finite treatment and/or functional cure. The follow-up time and measurements of clinical efficacy that need to be available at the time of marketing authorisation application will be dependent on the treatment approach, the endpoint chosen, the mechanism of action and the half-life of the drug. In addition, appropriate post-marketing long-term follow up of clinical outcomes should be planned for and agreed at the time of marketing authorisation. It is especially important that incidences of hepatic failure, liver decompensation, hepatocellular carcinoma and liver related death should be captured and reported.

Criteria to define a durable response on-treatment should include long-term sustained virological and biochemical response on treatment for up to 196 weeks, including monitoring of HBsAg levels, HBsAg seroconversion to anti-HBs.

Criteria for defining a durable response off-treatment should include long-term follow-up for up to 196 weeks of the sustained virological and biochemical response, including sustained HBsAg loss with or without HBsAg seroconversion to anti-HBs. In the future, clearance from cccDNA from the liver may be included in this endpoint.

The outcome of HBeAg, serum ALT and HBV DNA levels should be followed up regularly for both regimens aiming at finite or chronic suppressive treatment approaches to ensure sustained response and identification of break-through infection. Any late post-treatment relapses should be documented and investigated.

If an IP has shown convincing effect in one population, it may be possible to recommend the use of the same or an alternative posology based on safety and on pharmacokinetic/pharmacodynamic data demonstrating comparable plasma exposure in another population, e.g. paediatrics.

Sterilising cure defined as HBsAg-negative, HBsAb-positive or negative, HBeAg-negative, undetectable serum HBV DNA, undetectable cccDNA, no integrated HBV DNA and no histologic evidence of progressive liver disease is currently not considered achievable. Furthermore, the lack of standardised, validated assays able to evaluate the elimination of cccDNA and the potential need to obtain liver biopsies may limit trial feasibility. However, advances in the identification of biomarkers and standardisation of assays may support future re-evaluation of this endpoint. Sponsors wishing to pursue this endpoint are advised to consult with EU regulators early on in their clinical development programme.

5. Study design

5.1. Pharmacology studies

5.1.1. Pharmacokinetics

The pharmacokinetics of the IP should be evaluated in healthy volunteers and patients with chronic hepatitis B in different stages following the existing ICH E1A guideline on the extent of population

exposure to assess clinical safety for drugs (CPMP/ICH/375/95), the EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02), the EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/725881/2015) and the EMA guideline on pharmacokinetic studies in man (CHMP/EWP/147013/04). The pharmacokinetic profile should also be investigated in patients with advanced hepatitis B disease, if the IP is intended for decompensated patients. Pharmacokinetics (PK) in patients with various degrees of hepatic impairment should be investigated with each IP. The population studied should reflect the target population for treatment and any non-clinical data relevant to hepatotoxicity.

In case of combination therapy, additional pharmacokinetic data on mono-components and the combination should be considered in line with the EMA guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017).

5.2. Therapeutic studies

5.2.1. Exploratory and dose finding studies

Exploratory trials should characterise the safety and pharmacokinetics of IPs and should determine whether there are dose-limiting safety issues.

Antiviral activity of DAAs should be investigated in Phase 2 to provide clinical proof of concept. The PK data obtained should be analysed in light of one or more non-clinical pharmacokinetic-pharmacodynamic targets (PDTs) to guide dose selection for pivotal efficacy studies using a modelling and simulation approach. These studies and information of exposures coming from PK and pharmacodynamic (PD) studies that measure target engagement, and changes in HBsAg, HBV DNA, HBV RNA, and serum hepatitis B core-related antigen (HBcrAg) decline can be used to support dose selection for subsequent phase 3 trials.

As appropriate, there should be adequate pharmacodynamic data generated to support any plans for combinations of anti-HBV treatments. For example, by documenting the effect of short-term monotherapy and combined therapy on HBV DNA levels in untreated patients.

5.2.2. Confirmatory studies

Randomised double-blinded clinical trials are required to establish efficacy.

It is expected that the IP will be tested against an EU approved active comparator. Placebo-controlled clinical studies may in certain circumstances be considered acceptable, i.e. if a study is conducted in a study population that currently lacks a recommendation for treatment or in the case of add-on studies in which the IP plus an approved product is compared with placebo plus the approved product. Sponsors are advised to seek EMA scientific advice if they are planning to conduct a placebo-controlled study to justify the inclusion of a study population for whom CHB treatment is not recommended by official treatment guidelines.

The appropriate clinical study design of confirmatory studies for treatment of CHB are depending on whether the IP is intended for chronic suppressive therapy, finite treatment or functional cure, the mechanism of action and the half-life of the drug. Clinical trial considerations for of chronic suppressive (section 5.2.2.1), finite treatment (section 5.2.2.2) and functional cure (section 5.2.2.3) approaches are discussed separately in the section below.

5.2.2.1. Chronic suppressive treatment

Trial design

For products intended to achieve viral suppression on-treatment, the primary objective is usually to demonstrate non-inferiority vs. an active comparator for the primary endpoint using a non-inferiority margin that is adequately justified and ideally pre-discussed with EU regulators. However, if the sponsor intends to add a test agent to a licensed suppressive treatment to achieve an even lower HBV DNA level, the aim must be to demonstrate superiority vs. placebo when each is added to the licensed regimen.

The selection of the EU licensed active comparator should take into account the standard of care at the time the trial is initiated.

Primary endpoints

In clinical trials comparing the test agent with an approved active control arm, the primary efficacy endpoint should be sustained undetectable HBV DNA (i.e. treatment response) after 48 weeks on-treatment. Adequate follow-up data to demonstrate long-term sustained DNA suppression on treatment should be provided at least at week 96, week 144 and week 196.

For a superiority trial design, HBV DNA suppression is not acceptable as the sole primary efficacy endpoint because the clinical relevance of achieving a further reduction in HBV DNA (from low to very low) is unknown. If this is the aim, sponsors should seek scientific advice on potentially acceptable additional primary endpoints when planning efficacy trials.

Secondary or exploratory endpoints

Assessment of the progression of liver disease is important and may be based on non-invasive imaging methods together with serum biomarkers. Endpoints to consider include change in Model for End Stage Liver Disease scores (MELD), change in Child-Turcotte-Pugh scores, non-invasive markers of fibrosis (elastography or biomarkers), progression to liver failure requiring transplantation or resulting in death or occurrence of HCC.

Laboratory parameters such as ALT, serum bilirubin, PK and serum albumin levels at predefined time points should be designated as secondary endpoints. The median (range) change from baseline in these parameters and the proportion of patients with normalised values should be documented.

Patient reported outcome measures can be considered as secondary or exploratory endpoints in confirmatory studies.

5.2.2.2. Finite treatment

Trial design

For IPs aiming to achieve sustained viral suppression off-treatment the primary objective is usually to demonstrate superiority either to an EU approved active comparator or placebo. Alternatively, a randomised controlled add-on superiority study in virologically suppressed patients or a superiority study to placebo may be considered appropriate in patients in whom treatment is currently not indicated according to current treatment guidelines. The latter should be adequately justified and pre-agreed with EU regulators.

For finite treatment approaches all therapies should be discontinued after a pre-defined treatment duration. Sponsors may choose to evaluate stopping only the candidate regimen or stopping all anti-

HBV treatment at least in those who have met the predefined criteria. The sustained response off-treatment should be investigated for at least 24 weeks after treatment discontinuation. However, the follow-up period for sustained clinical response and safety should be up to 196 weeks and is depending on the mechanism of action and the half-life of the IP.

Primary endpoint

For finite treatment approaches the primary endpoint should be sustained HBV DNA suppression for at least 24 weeks off-treatment.

It is important to note that sustained HBV DNA suppression at least 24 weeks off-treatment will not be an appropriate primary efficacy endpoint to allow functional cure claims but will support an indication for a finite treatment duration with the aim of HBV DNA suppression off-treatment.

Secondary or exploratory endpoints

See section 5.2.2.1 regarding possible secondary and exploratory endpoints.

5.2.2.3. Functional cure

Trial design

With no currently approved products to achieve functional cure, the primary objective of a clinical trial is expected to demonstrate superiority for the test regimen versus the comparator for the primary endpoint related to functional cure (see below).

Such a trial may be conducted in virologically suppressed patients who are randomised to add-on treatment with the candidate regimen or placebo. However, if the regimen intended to achieve functional cure is also suitable to achieve or maintain viral suppression, the patient population may differ accordingly. Alternatively, such a trial may be conducted in patients in whom viral suppressive treatment is currently not recommended according to treatment guidelines.

Specific considerations for stopping treatments

It is expected that the candidate regimen will be discontinued after a pre-defined treatment duration. Sponsors may choose to evaluate stopping only the candidate regimen or stopping all anti-HBV treatment at least in those who have met the functional cure definition. Importantly, if only the candidate regimen is stopped, this will not allow functional cure claims.

The criteria for stopping NUC therapy should be based on clinical evidence and on recommendations made by expert professional bodies. In principle, stopping background NUC therapies in virally suppressed patients should not pose an undue safety risk for patients. If NUCs are to be stopped, this should be equally applied in all treatment arms according to the same well-defined pre-specified criteria. It is recommended that these criteria (e.g. sustained HBV DNA suppression and sustained HBsAg loss with or without responses based on other biomarkers) are discussed with EU regulators prior to the study start.

Baseline demographic and disease characteristics that could affect efficacy endpoints after stopping NUCs should be considered in the study protocol (inclusion/exclusion criteria, stratification criteria and pre-defined subgroup analyses). Variables to consider include HBeAg status, HBsAg levels at baseline and at the time of stopping NUCs, duration of viral suppression, treatment history (duration and type of NUC therapy), presence/absence of cirrhosis, age, race (Asian/Caucasians), HBV genotype and HBV DNA levels during reactivation.

Also, variables that could reduce the safety risk for patients should be considered. These may include end-of-treatment (EOT) HBsAg below a pre-specified level, prior NUC therapy and the off-therapy HBV DNA kinetics.

Sponsors should predefine a stringent monitoring plan for hepatitis flares and criteria for restarting NUC treatment. For further considerations for monitoring safety please refer to section 6.

Primary endpoint

For finite treatments aimed to achieve functional cure, the co-primary endpoint should be sustained HBV DNA suppression and HBsAg loss with or without HBs seroconversion after at least 24 weeks off-treatment. Both components of the endpoint need to be met at week 24 after treatment cessation and additional follow-up of up to 196 weeks to monitor for the durability of response off-treatment is required.

The use of primary efficacy endpoints other than HBV DNA suppression and HBsAg loss (e.g. reductions in HBsAg levels from baseline or cccDNA clearance) is currently not recommended because they have unknown clinical relevance. Sponsors interested in using alternative primary efficacy endpoints should discuss the evidence base and any relevant clinical trial results with EU regulators before initiating phase 3 clinical development.

Secondary or exploratory endpoints

See section 5.2.2.1 regarding possible secondary and exploratory endpoints.

5.2.2.4. Follow-up

Long-term follow up (i.e. after the primary endpoint has been determined) of clinical outcomes is required to ensure sustained clinical response whether the aim is viral suppression, finite treatment and/or functional cure. Therefore, appropriate follow up time of clinical outcomes must be planned and agreed within the study protocol. In addition, additional post-marketing long-term FU should be planned and agreed at the time of marketing authorisation. It is especially important that incidences of hepatic failure, liver decompensation, hepatocellular carcinoma and liver related death are captured and reported.

5.2.2.5. Resistance development

Data on resistance development and late-post treatment relapse is an important part of the clinical development programme and long-term follow up. Therefore, the development of clinical resistance should be monitored at baseline, on-treatment and during pre-defined intervals if long-term therapy is planned and during the long-term follow-up. Genotypic and phenotypic analyses should be conducted for all patients with virological failure or late-post treatment relapse. Therefore, a detailed resistance monitoring and management plan and a resistance analysis plan should be included in the study protocol.

5.2.2.6. Statistical considerations:

Sponsors should consider stratifying for prespecified baseline factors that are anticipated to be prognostic for treatment outcome, e.g. HBeAg status, HBV DNA level and HBsAg level.

Stopping treatment in clinical trials

Statistical considerations for studies investigating stopping treatment that may result in imbalances between the treatment arms and introduce bias in favour of the test arm, should ideally be discussed with EU regulators before the study start.

In addition, aspects such as the handling of intercurrent events and defining the appropriate estimand, especially in relation to treatment discontinuation and outcome interpretation in line with the recommendations outlined in the ICH E9(R1) Step 5 Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017) should also be considered.

6. Safety aspects

Safety monitoring in clinical trials should reflect what is known about the mechanism of action of the IPs. For example, safety concerns associated with immune modulatory therapies are immune-mediated hepatitis flares and autoimmunity (e.g. immune-related adverse events observed with checkpoint inhibitors).

Monitoring of hepatitis flares (elevation of ALT levels to more than 10 times the upper limit of normal and more than twice the baseline value) should be conducted to identify potential drug induced liver injury and flare related morbidity. This is particularly important, in case chronic NUC therapy is stopped in combination therapies aiming at functional cure. Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV therapy, particularly in the absence of HBsAg loss. Therefore, sponsors should predefine a stringent monitoring plan for well-defined hepatitis flares during and after stopping therapy and criteria for restarting NUC treatment to reduce the safety risk of patients. Severe flares are usually associated with increase in bilirubin or prothrombin time, can be serious and life-threatening and require prompt treatment. Therefore, patients should be monitored closely with laboratory and clinical follow up after stopping anti-HBV treatment.

If it is proposed to stop NUCs in the absence of HBsAg loss, sponsors should pre-define eligibility criteria for stopping NUCs that minimise the risk of flares. These may include end-of-treatment (EOT) HBsAg below a pre-specified level, prior NUC therapy and the off-therapy HBV DNA kinetics. The duration of follow up after stopping NUCs should be based on the mechanism of action and the half-life of the drug. The safety profile observed in early phase trials should guide the monitoring plan for late phase trials.

Treatment reinitiation criteria should reflect current guidelines from expert professional bodies. For example, reinitiation of NUC therapy may be considered in patients with HBV DNA >10,000 IU/mL independent of ALT levels and the latest in all patients with HBV DNA >100,000 IU/mL.

A DSMB, in line with the recommendations outlined in the ICH E6(R2) and the EMA guideline on data monitoring committee (EMEA/CHMP/EWP/5872/03 Corr), is strongly recommended to monitor, review and judge cases of hepatitis flares and to inform about restarting of NUC treatments.

The safety database needed to extend the use of a drug that is approved for the use in patients without cirrhosis or with compensated cirrhosis to patients with decompensated cirrhosis is dependent on the safety profile of the IP and the overall benefit/risk profile for the intended population.

7. Studies in special populations

7.1.1. Patients with HBV/HIV-1 coinfection

Reflecting standard of care for persons living with HIV, the great majority of such persons in the EU are virologically suppressed on treatment and do not have immune suppression that could interfere with the HBV disease course. Therefore, HBV/HIV co-infected individuals who are responding well to their antiretroviral therapy may potentially be enrolled in the same trials as those with HBV mono-infection.

However, if such individuals rely on certain NUCs both as part of their antiretroviral therapy and for HBV suppression, they would not be suitable for enrolment into trials in which it is proposed to stop NUC treatment subject to meeting specific HBV-related criteria, as this may increase the risk of HIV viral rebound and horizontal/vertical transmission and the risk of HBV rebound and hepatitis flares.

7.1.2. Patients with HBV/HDV co-infection

If patients with HBV/HDV coinfection are enrolled in a clinical study for the treatment of CHB, randomisation should be stratified accordingly given the potential for different safety and efficacy in co-infected vs. HBV mono-infected individuals.

Recommendations for trials in patients with HBV/HDV coinfection with the aim to treat both diseases are beyond the scope of this guideline. Sponsors, following a clinical development plan to address both diseases should discuss their plans with the EU regulators.

7.1.3. Patients with HBV/HCV co-infection

It is recommended that patients with HBV/HCV co-infection are not enrolled into trials aimed at treatment of CHB. Such patients may be enrolled after receiving treatment that has successfully cleared HCV.

7.1.4. Studies in elderly patients

It is recommended that pivotal trials allow inclusion of patients aged >65 years unless there are non-clinical or clinical data suggesting that there are specific concerns regarding the use in older adults and/or it seems necessary to obtain further safety and/or PK data to confirm an appropriate dose regimen for this age group. If included, the data should be reported descriptively according to age strata (e.g. 65-74; 75-84; >85 years).

7.1.5. Studies in pregnant and breastfeeding women

Given the physiological changes during pregnancy, there is a critical need to ensure the adequacy of the validated dose in adults in this group of patients. Therefore, collection of PK data to confirm that the PK of the drug is not significantly altered during pregnancy is strongly encouraged. As it is not expected that clinical efficacy will differ from non-pregnant adults, dedicated clinical efficacy will not be required. Adequate follow up of the mother child pair in line with the EMA guideline on risk assessment of medicinal products on human Reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005) should be planned.

7.1.6. Studies in paediatric patients

Hepatitis B infection in children differs from the disease in adults in many aspects such as the route of transmission (being mainly mother to child), host immune response, the natural course of disease that is generally asymptomatic or mild during childhood, the rates of chronicity and the higher rate of spontaneous remission.

Due to the differences between children and adults, extrapolation of efficacy from adults to patients less than 12 years of age may not be possible in all scenarios and should be considered case by case depending on the mechanism of action of the medicinal product, the treatment approach and the age group to be investigated. Separate efficacy studies in children may be needed. Therefore, sponsors are advised to discuss their paediatric plans upfront with EU regulators.

In contrast, unless there are any specific safety issues identified from non-clinical or adult clinical studies, adolescents can be enrolled into phase 3 efficacy trials. In such cases, it is recommended that sponsors ensure that the final population PK analyses include sufficient adolescent PK data to assess any differences vs. adults. Alternatively, sponsors may conduct a dedicated adolescent study in parallel with the phase 3 study in adults. Principles are outlined in the following guidelines: ICH E11(R1) Guideline on clinical investigation of medicinal products in the paediatric population (EMA/CPMP/ICH/2711/1999), EMA guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum), EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/1897724/2018) and ICH guideline E11A on paediatric extrapolation (EMA/CHMP/ICH/205218/2022).

Considering the complexity that these studies could have, sponsors are recommended to consult EU regulators early in the development regarding their plans for paediatric studies

8. Definitions

Nomenclature for chronic hepatitis B

Table 1 Phases of chronic HBV infection (taken from the EASL 2025 Clinical Practice Guidelines)

	Phase 1	Phase 2	Phase 3	Phase 4
	HBeAg-positive chronic infection	**HBeAg-positive chronic hepatitis**	**HBeAg-negative chronic infection**	**HBeAg-negative chronic hepatitis**
HBsAg	High	Intermediate to high	Low, usually <1,000 IU/ml	Intermediate, usually >1,000 IU/ml
HBV DNA	High, usually $\geq 10^7$ IU/ml	Moderate to high, usually 10^4-10^7 IU/ml	Usually <2,000 IU/ml	Usually, >2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease progression (if untreated)	None/minimal	Moderate to severe	None	Mild to severe

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
*Either persistently or intermittently.

Definition of HBV cure, as considered in this guideline

- Partial cure:

  Sustained HBV DNA suppression 24 weeks off-treatment. Sustained HBV DNA < LLOQ, 24 weeks after treatment cessation.

  At present, the addition of sustained HBsAg levels <100 IU/mL to the partial cure definition is not considered acceptable because there is at the time of writing this guidance not yet sufficient clinical data available to validate that HBsAg decline to < 100 IU/mL is a clinically

meaningful surrogate marker. Inconsistent correlations between qHBsAg and clinical response have been reported.

Also, for chronic treatment approaches applicable. In this case, sustained HBV DNA suppression < LLOQ on-treatment with sufficient long-term follow up.

- Functional cure

Functional cure is defined by sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) with or without anti-HBs seroconversion, at least 24 weeks after treatment discontinuation with sufficient follow-up time.

- Sterilising cure

Sterilising cure is defined as HBsAg-negative, HBsAb-positive or negative, HBeAg-negative, undetectable serum HBV DNA, undetectable covalently closed circular DNA (cccDNA), and no integrated HBV DNA and no histologic evidence of progressive liver disease. Currently, sterilising cure is not considered possible with the treatments in development.