Journal of Virus Eradication 9 (2023) 100344

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

Original research

Design and analysis considerations for early phase clinical trials in hepatitis B (HBV) cure research: the ACTG A5394 study in persons with both HIV and HBV

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ARTICLE INFO

Keywords:
HBV
HIV
Cure
Clinical trial design
Placebo
TLR agonist

ABSTRACT

With growing interest and efforts to achieve a hepatitis B (HBV) cure, HBV therapeutics have increasingly entered the clinical testing phase. In designing an early phase clinical trial aimed at HBV cure, the heterogeneity in participants and the choice of a biomarker endpoint that signals a cure requires careful consideration. We describe the key elements to consider during the development of HBV clinical trials aimed at a functional cure, and how we have addressed them in the design of a phase II AIDS Clinical Trials Group (ACTG) study, A5394 (NCT05551273). The trial we present is for persons with both HIV and HBV, a unique population that has much to gain from an HBV cure. Our decisions on the design elements are specific to the study agent and the targeted population, but our deliberations may be informative in the emerging field of early phase HBV trials aimed at cure.

1. Introduction

Recent scientific advances suggest that an hepatitis B (HBV) functional cure is possible, with clinical trials investigating novel drugs and new strategies underway.[1] The first-line antiviral therapy for chronic hepatitis B virus (CHBV) consists of nucleos(t)ide reverse transcriptase inhibitors (NRTIs), and, while safe and efficacious, treatment is typically lifelong. A finite therapy leading to a cure will reduce the associated burdens of ongoing adherence and disease monitoring. The ultimate goal is a complete sterilizing cure, defined as an undetectable hepatitis B virus surface antigen (HBsAg) in serum and complete elimination of HBV cccDNA (covalently closed circular DNA) and integrated DNA from liver cells.[2] A pragmatic endpoint at this time is a "functional cure", defined as the sustained loss of HBsAg with undetectable viral DNA, preferably with antibodies against the antigen (anti-HBs) after completion of a finite course of treatment.[3] Functional cure occurs with spontaneous resolution of acute HBV infection.

Newly identified drug targets, compounds and strategies have led to a number of clinical trials for HBV cure, and we will likely see more promising drugs moving along the development pipeline. Clinical trials at this juncture are still mostly aimed at dose selection and combinations of drugs for safety and signals of efficacy. Similar to HIV cure research,[4] embedded in these, HBV trials are innovative studies to characterize correlates of "cure", identify characteristics associated with success, and refine endpoints according to the mode of action of the investigational drug. In both HIV and HBV cure trials, an intervention with few adverse effects and high efficacy is desirable, given the excellent prognosis for people living with HIV or HBV on antiviral therapy. New therapies need to have excellent safety profiles and achieve beneficial outcomes to justify the additional risk.[5]

Hepatitis B cure is one of the focuses of the NIAID-funded clinical trials network, the AIDS Clinical Trials Group (ACTG). We present the design of a phase II ACTG trial, the A5394, to describe key elements to consider during the development of HBV clinical trials aimed at a

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https://doi.org/10.1016/j.jve.2023.100344
Received 14 April 2023; Received in revised form 18 August 2023; Accepted 23 August 2023
Available online 24 August 2023

functional cure and how we have addressed them. The A5394 study will evaluate an oral toll-like receptor (TLR) 8 agonist, selgantolimod, and its effect on HBsAg in persons with HIV and chronic HBV and on suppressive antiviral therapy with NRTIs that are active against both HIV and HBV. The TLRs have a critical role in the host response to viruses by initiating intracellular signaling pathways to induce antiviral mediators. TLR8 agonists have a potential role of reducing HBsAg production by inducing immunomodulatory and antiviral cytokines. People with HIV (PWH) are typically excluded from HBV cure trials despite having much to gain from functional cure for HBV. This is an opportunity to evaluate HBV cure in a population with high medical needs. In the United States and Europe, considered regions with low HBV prevalence, approximately 7–10% of PWH have evidence of chronic HBV infection,[6] which represents a 10–20-fold higher prevalence than in the population without HIV.[7]

In this paper, we discuss the key features of the A5394 study (ClinicalTrials.gov, NCT05551273) including the study population, primary endpoint, sample size, and safety considerations, and how they are aligned together in the trial design. We include estimand-analysis tables for the primary objectives, following the latest guidance from The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Addendum E9 (R1) on estimands and sensitivity analyses.[8] We conclude with a discussion on the current challenges of trial designs for HBV cure research and highlight the importance of customizing each design for the specific objective of the study compound.

2. Study design

2.1. Study population

People with HBV are highly heterogeneous, and early phase clinical trials in HBV functional cure research require careful consideration of the targeted study population. Challenges include identifying a population with HBV characteristics that align with the study drug mechanism of action, as well as considering a population who will benefit the most from cure research in the current landscape of HBV investigational agents. The report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference[9] describes prioritization of study populations with consideration for HBV disease status and management under current therapies, and special populations with cirrhosis, liver transplantation or HIV, and children. Characteristics of potential importance that are based on laboratory tests include HBV DNA, quantitative HBsAg (qHBsAg) and/or ALT levels, and HBeAg status. This list will likely increase as HBV biomarker science evolves. Due to the concerns about the potential for HBV flare leading to liver inflammation,[10] the FDA final guidance on HBV drug development has outlined an approach to evaluating adults without cirrhosis in early phase clinical trials.[11] Another important factor to consider is the duration of existing NRTI therapy since prolonged suppression of HBV replication is associated with reduction in the amount and transcriptional activity of cccDNA.[12]

The characteristics of the targeted study population inform decisions on the study design and the assumptions for the sample size determination. In the A5394 study, we aim to evaluate selgantolimod in people with HIV and HBV on effective HBV-active antiretroviral therapy (ART), with HIV-1 RNA and HBV DNA below the lower limits of quantification in plasma. The study population has been on NRTI-containing ART for at least 5 years but with qHBsAg >1000 IU/mL (3 log10), targeting individuals who have not been able to reduce qHBsAg to a very low level despite several years of NRTI treatment and restoration of immune function with treatment of HIV. The $CD4^+$ T cell count requirement for the study is $\geq$ 350 cells/mm^3. Studies have shown that qHBsAg declines are most evident within the first year of therapy, with levels remaining stable afterwards.[13] Reported annual rates of HBsAg loss among individuals with HBV and HIV on NRTI treatment range from 0.6 to 6% per year, with the highest rates of clearance in the first few years of treatment in the setting of immune restoration.[13–16] Hence, our study targets a population that is unlikely to achieve further qHBsAg reduction with NRTIs alone. The role of the HBeAg status is unclear, and since those individuals with and without HBeAg differ markedly with respect to HBV dynamics and immune responses, observations of drug effect in one group may not be observed in the other. Accordingly, we have decided to include one-half of the participants with positive HBeAg. We also target individuals without evidence of liver fibrosis or cirrhosis, based on the potential for HBV flare when individuals mount a robust HBV immune response.

2.2. Primary objective, outcome and hypothesis

HBsAg loss confirmed on two occasions, at least 6 months apart, is recommended as the primary endpoint for phase III trials in HBV cure.[9] For exploratory, early phase trials, a substantial level of decline in serum qHBsAg may be appropriate, since HBsAg loss is preceded by a decline in qHBsAg level. While HBsAg loss is the preferred outcome, a lower bar in an early phase trial minimizes the risk of abandoning promising drugs that may be successful in combination with other drugs to achieve HBV cure. Additionally, an important consideration in framing the study question in HBV cure is that HBsAg in the blood may be derived from cccDNA or integrated HBV DNA,[17] and achieving HBsAg loss would depend on the mechanism of action of the investigational agent. For example, a reduction in the production of cccDNA-derived HBsAg would not lead to complete HBsAg loss if production from integrated HBV DNA persists, and vice versa. This heterogeneity has the potential to mask a promising drug effect in early phase trials if HBsAg loss is the primary objective.

These considerations have led to the A5394 primary objective to evaluate the decline in qHBsAg when a TLR8 agonist is added to a NRTI-based ART. The decline can be defined as a continuous variable on the individual qHBsAg change from baseline at the end of treatment, or as a binary variable indicating a decreased level of clinical interest. For HBV cure trials, an important consideration in the choice of primary outcome is potential heterogeneity of the study population. There may be only a subset of individuals who respond favorably to the study agent, whose characteristics are unknown at the time of the trial design. An overall summary of a continuous measure, such as the mean of the qHBsAg changes, can dilute the treatment effect that is present only in a small subset. In this setting, a binary endpoint indicating whether or not the decreased level of clinical interest has been achieved for each individual would be easier to interpret than a continuous measure from a mixture distribution of two very different subpopulations of different sizes. For the A5394 study, we have decided on a binary endpoint indicating a decline of at least 1 log10 in qHBsAg as a promising signal, consistent with the recommendation in Ref. 9. We anticipate a small proportion of 8%[18] of participants to achieve this decline in this test-of-concept trial, leading to 36 participants receiving the study treatment for a single-arm evaluation (details to follow in Section 2.4). A number of other HBV markers will be studied as secondary and exploratory, including qHBsAg changes throughout the study, HBsAg loss, anti-HBs gain, hepatitis B core-related antigen (HBcrAg), HBV RNA, qHBeAg and HBsAg isoforms (large, medium and small).

2.3. The role of placebo

The importance of concurrent controls and blinding in a trial depends on multiple factors, including the study objectives and the extent to which the study procedures and outcome assessments are subject to potential bias. A concurrent control group may be particularly valuable for trials in diseases where the natural history is not well-characterized, or for trials that enroll individuals with a wide range of disease severity. However, in early phase trials, a concurrent control group with blinding is generally not as critical as it is for a confirmatory efficacy trial, and rigorous inference from comparison to a control (e.g., placebo) may not

be necessary.[19] A control group can still be useful in this setting to facilitate the interpretation of the safety data and provide a comparator for exploratory assessments of activity or efficacy.

While the FDA generally recognizes internally controlled study designs where "the control group and test groups are chosen from the same population and treated concurrently",[19] there are settings where the use of external controls (including historical controls) may be not only acceptable but advisable. A recent review on the use of external controls lists various circumstances where external control designs without concurrent controls may be acceptable,[20] and the ICH E10 guidance about the choice of control groups describes general principles involved in choosing a control group for clinical trials intended to demonstrate treatment efficacy.[21] Important considerations include minimization of bias, ethical and practical issues associated with the trial design, and the quality of inference from the trial results. Minimizing the potential impact of regression to the mean is also important.[22]

The use of external control design may be appropriate in the HBV cure research setting. Chronic HBV disease progression is well understood and predictable, and the outcome that is a laboratory measure, such as HBsAg, is objective. The treatment effect is expected to have a temporal association with administration of the investigational product, and the decreased qHBsAg provides compelling evidence of change in the established progression of disease.

In the A5394 study, we do not expect a substantial qHBsAg decline without additional intervention in the study population based on the data from external cohorts. A Thai cohort study[23] follow-up of 18 individuals who had qHBsAg >1000 IU/ml after 3 years of NRTI-based treatment showed that none had a decline ≥1 log10 IU/mL a year later (J. Audsley, personal communication, July 27, 2020). In a similar cohort from the ACTG,[24] none of the 38 participants with qHBsAg >1000 IU/mL after 96 weeks of NRTI-based treatment had ≥1 log10 reduction after 24 additional weeks of treatment at week 120. Therefore, we plan to conduct the primary qHBsAg analysis as a single-arm analysis to assess promising activity in qHBsAg reduction. It has been designed to reject a rate that is nearly zero in attaining a ≥1 log decrease (planned null rate of 0.5%), derived from external studies. A study design based on the comparison of the qHBsAg decline between the active and placebo arms will require a large sample size that is not justifiable at this exploratory stage. Although a placebo arm will not serve as a control for the statistical comparison of the primary outcome, we have decided to include a placebo arm of 12 participants after considering the advantages. One purpose of the placebo arm is to provide further evidence that no one achieves ≥1 log10 IU/mL decline in qHBsAg in the absence of a new intervention. The probability of observing one or more participant with this decrease among 12 placebo participants is only 6% when a 0.5% rate is assumed. Another purpose for a placebo is to serve as a control group in the analyses of exploratory biomarkers. The placebo arm will also help to control bias when assessing safety (Section 2.5 below).

2.4. Type I error, power and sample size

A key objective of many early phase trials is to provide preliminary evidence of activity or efficacy, and such assessments are usually exploratory. Early in clinical development, the initial target population of interest might place a practical limit on the sample size. The availability of the proposed study population or the drug supply may limit the sample size, and a sample size that is feasible but still adequate to meet the study objectives is needed.

There are two types of errors when we test the concept of whether the novel treatment provides improvement over the existing one. On one hand, the new treatment may appear better than the existing one when it is not in truth better (type I error). The observed improvement may be due to chance factors in participant selection. On the other hand, the new treatment may appear not better than the existing one and may be rejected for further study, when in fact it is better (type II error). Large trials minimize both error probabilities at the cost of large sample sizes. For a trial in early development, the type I error - that of making false positive claims about a new treatment – can be deemed less consequential, because the results of a successful early trial will be followed up by large confirmatory trials. The type II error is more serious in an early test-of-concept study. We want to be cautious not to reject a treatment that offers benefits. For the non-randomized pilot studies to determine whether a new treatment should proceed to a large controlled trial, a reasonable choice of error rate for the type II error - that of rejecting a promising treatment - has been suggested to be no more than 10%.[25] For the type I error, a more relaxed threshold of up to 25% has been suggested.

As a test-of-concept study, the type I error in the A5394 study is relaxed to 1-sided 5% (rather than 2-sided 5% in most trials) for the primary analysis of qHBsAg decline. Positive findings will be investigated further in future trials. On the other hand, the power is set high at nearly 90% (corresponding to 10% type II error) so that there is a low probability of missing a promising result. These trial error rates and the assumed rate of 8% (Section 2.2) to reject the null rate of 0.5% (Section 2.3) lead to 36 participants for a single-arm evaluation. To include placebo recipients for the purpose of safety monitoring and exploratory biomarker analyses, 48 study participants will be randomized 3:1 to receive the TLR8 agonist selgantolimod (36 active and 12 placebo), with randomization stratified by HBeAg status.

2.5. Safety interim monitoring

The FDA recommends well-defined criteria for monitoring hepatitis flares or HBV reactivation in addition to the routine safety monitoring in HBV clinical trial protocols.[11] They should include predefined algorithms for data collection in the setting of significant hepatic events to ensure that the relevant data is available for further assessment. The outcomes for all serious hepatic events should be systematically assessed during clinical development,[10] and evaluation by an independent committee is encouraged.

While there are no known concerns about hepatic flares or other serious adverse events (AEs) to date from prior clinical trials with selgantolimod, the A5394 team has developed safety criteria based on the accumulating AEs while the study treatment is ongoing. An AE review by an independent Study Monitoring Committee (SMC) will be triggered if any of the criteria are not met. Table 1 presents the criteria and probabilities of passing the safety criteria in 36 participants receiving the active treatment. They are aimed at a low probability of passing the safety criteria when the true AE rates are unacceptably high and a high probability of passing the criteria to proceed when the true AE rates are acceptably low. Such calculations can be useful in determining if the sample size is reasonably adequate to detect serious adverse events that should pause the trial for further assessments or lead to trial termination.

The trial can benefit from inclusion of placebo recipients for safety monitoring, which allows AEs to be assessed while blinded to treatment assignment. Treatment blinding to the participants, providers and study team can alleviate potential biases about the treatment in the evaluation and reporting of AEs. The SMC will review the relationships of the event (s) to study treatment as assessed by the participant's provider and the blinded study team. The committee can become unblinded to the study treatment to assess the safety criteria and recommend how the study should proceed with respect to resuming enrollment and continuing study treatment.

2.6. Estimands and planned analyses

The ICH E9 (R1) Addendum on "Estimands and Sensitivity Analysis in Clinical Trials" introduced a framework that guides clinical trial researchers in specifying the treatment effect precisely and transparently. The guidance reinforces the importance of clearly defining the estimand and aligning the proposed design and analysis with the trial objective.

Table 1
Safety criteria for adverse events and the probabilities of passing the criteria based on 36 participants in A5394. The worst AE outcome from each participant would be considered for the safety criteria. The probabilities are calculated from multinomial distributions.

	Grade 3 AEs	Grade 4 AEs	Deaths	
Guideline	≤2 participant experience Grade 3 adverse event (AE) that is deemed related to the study product as judged by the Core Team and subsequently reviewed by the SMC, based on the site attribution.	≤1 participant experience a Grade 4 AE related to the study product as judged by the Core Team and subsequently reviewed by the SMC, based on the site attribution.	None of the participants with death attributed to the study product as judged by the Core Team or the site, subsequently reviewed by the SMC.	
Probabilities	True probability of grade 3 AE	True probability of grade 4 AE	True probability of death	Probability of passing safety criteria
	0.15[a]	0.10[a]	0.010[a]	<1%[a]
		0.05	0.010	2%
	0.10	0.05	0.010	8%
			0.005	10%
	0.05	0.02	0.005	51%
	0.03	0.01	0.005	72%
	0.01[b]	0.01[b]	0.005	79%
			0.003	85%
			0.001[b]	91%[b]

[a] As an example, if the true proportion with Grade 3 AEs is as high as 15%, and the proportions are 10% for Grade 4 events and 1% for deaths, then there is a very low probability of <1% of passing the safety criteria. Assuming that these are unacceptable rates, there is a very low probability of incorrectly passing the safety criteria.

[b] In another example, if the true proportion with Grade 3 AEs is as low as 1%, the true proportion with Grade 4 adverse events is also low at 1%, and the true proportion of death is as low as 0.1%, then there is a high probability of 91% of passing the safety criteria to proceed with the study. Assuming that these are acceptable adverse event rates, there is a high probability of correctly passing the criteria.

There have been numerous articles about estimands,[26–29] including a recent review which showed that the description of estimands in published trial protocols is poor,[30] urging for clarity in trials.

We have defined estimands and their associated analysis plans for the primary A5394 study objectives on safety and qHBsAg. Table 2 presents the estimand (on the left) and the associated analysis plan (on the right) for the objective on safety. It is similar to the one presented in Ref. 31. Table 3 presents the estimand about the treatment effect on qHBsAg and the corresponding analysis plans, and additional details are provided in the Supplement.

Table 2
Estimand-analysis table for the primary objective on safety.

Primary objective on safety: To assess the safety of treatment with selgantolimod (SLGN) administered once weekly by mouth for 24 weeks.
Estimand description: Probability of experiencing at least one adverse event of moderate or higher severity over 24 weeks after initiation of SLGN in adults with both chronic HBV and HIV-1 who have been on HBV-active antiretroviral therapy (ART) for ≥5 years, yet have persistent and at least moderate level of hepatitis surface antigen.
Treatment: SLGN 3 mg once weekly for 24 weeks.

ESTIMAND	**ANALYSIS**
Target population	**Analysis set**
Adults with HIV-1 and chronic hepatitis B virus on suppressive antiviral therapy for HIV-1 and HBV for ≥5 years, with quantitative hepatitis B surface antigen (qHBsAg) > 1000 IU/mL, without evidence of advanced liver fibrosis or cirrhosis and with or without positive HBeAg, who initiate SLGN treatment.	All participants who meet the trial eligibility criteria and initiate SLGN treatment following randomization.
Variable	**Outcome measure**
Occurrence of at least one moderate, severe or life-threatening adverse event, or death over 24 weeks after treatment initiation.	Occurrence of Grade ≥2 adverse event (s), graded according to the NIAID DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, out to study visit Week 24, per protocol-defined visit window.
Handling of intercurrent events	**Handling of missing data**
• Premature treatment discontinuation: All adverse events through 24 weeks are used to determine the variable (Treatment Policy Strategy[a]). • Pregnancy: Women who become pregnant are followed off treatment and included. Events through 24 weeks are used to determine the variable (Treatment Policy Strategy[a]).	For participants discontinuing the study prior to Week 24, assume that no additional adverse events occur after the discontinuation. Sensitivity Analysis For participants discontinuing the study prior to Week 24, censor follow-up at the last study visit.
Population-level summary measure	**Analysis approach**
Proportion.	Proportion calculated along with two-sided 95% confidence interval (CI) using the Clopper-Pearson exact method for binomial data. Sensitivity Analysis Proportion estimated using the Kaplan-Meier method, with Greenwood's formula for the variance to calculate a 2-sided 95% CI.

[a] Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

3. Discussion

With growing interests and efforts in achieving HBV cure, HBV therapeutics have increasingly entered the clinical phase. In designing an early phase clinical trial aimed at HBV cure, there are several important factors to consider. First, the study population must be chosen carefully. Targeting the trial population with HBV characteristics that align with the study drug mechanism of action is important but may not be fully understood prior to the trial. The safety of the study agent and the potential for a beneficial outcome in the targeted population must be carefully weighed so that the potential additional risk is justifiable. Second, defining the achievable outcome that correlates with HBV cure is challenging and depends on the drug mechanism. What would be considered clinically meaningful may not be clear in an early phase trial, and aiming too high could jeopardize the future of a possibly promising therapeutic agent. Early phase trials often rely on biomarkers, and the choice of the biomarker can be unclear, especially when measured by a newly developed assay. Furthermore, there may be a constraint to keep the study small while promising drugs are explored, in light of the availability of the targeted population willing to participate in early phase clinical trials and the drug supply. These factors affected our decisions about the A5394 study design.

We have designed the A5394 study to assess the effect of the TLR agonist selgantolimod on reducing qHBsAg in persons with HBV and HIV who are unlikely to achieve further meaningful qHBsAg reduction

Table 3
Estimand-analysis table for the primary objective related to efficacy.

Primary Objective: To determine the proportion of participants with ≥1 log10 IU/mL decline in quantitative HBsAg (qHBsAg) after selgantolimod (SLGN) treatment at Week 24.

Estimand description: Probability of achieving qHBsAg decline ≥1 log10 IU/mL in qHBsAg from baseline to 24 weeks after initiation of SLGN in adults with HIV-1 and HBV who have been on HBV-active antiretroviral therapy (ART) for ≥5 years, yet have persistent and at least moderate level of hepatitis surface antigen.

Treatment: SLGN 3 mg once weekly for 24 weeks.

ESTIMAND	ANALYSIS
Target population	**Analysis set**
Adults with HIV-1 and chronic hepatitis B virus on suppressive antiviral therapy for HIV-1 and HBV for ≥5 years, with quantitative hepatitis B surface antigen (qHBsAg) > 1000 IU/mL, without evidence of advanced liver fibrosis or cirrhosis and with or without positive HBeAg, who initiate SLGN treatment.	All participants who meet the trial eligibility criteria and initiate SLGN treatment following randomization.
Variable	**Outcome measure**
Quantitative HBsAg (qHBsAg) decline ≥1 log10 IU/mL at 24 weeks after treatment initiation.	Binary outcome indicating quantitative HBsAg (qHBsAg) decline ≥1 log10 from baseline (Week 0) at study visit Week 24, per protocol-defined visit window. If there is more than one result in this visit window, the one closest to Week 24 will be used.
Handling of intercurrent events	**Handling of missing data**
• Premature treatment discontinuation: All measurements through 24 weeks are used to determine the variable (Treatment Policy Strategy[a]) • Pregnancy: Women who become pregnant are followed off treatment. Measurements through 24 weeks used to determine the variable (Treatment Policy Strategy[a]). • Death: If the cause of death is deemed unrelated to SLGN, then all measurements through 24 weeks are used to determine the variable. If the cause of death is deemed related to SLGN, death is considered a failure to achieve decline. (Composite Variable Strategy[b]).	• If a participant discontinues the study prior to Week 24 for reasons potentially related to the study treatment: a If no post-baseline result is available, then outcome is assigned as failure (<1 log10 decline). b If any post-baseline result is available, the prior result closest to Week 24 will be carried forward as the outcome. • If a participant discontinues the study prior to Week 24 for reasons clearly unrelated to the study treatment (e.g., participant moved away): a If treated for at least 12 weeks and result(s) at or after Week 12 is (are) available, the prior result closest to Week 24 will be used as the outcome. b Otherwise, missing completely at random is assumed. • If a participant's Week 24 result is missing while on study (e.g., missed visit), the prior result closest to Week 24 will be carried forward as the outcome. • If the baseline result is missing, then missing completely at random is assumed.
Population-level summary measure	**Analysis approach**
Proportion.	Proportion with a two-sided 95% confidence interval (CI) using the Clopper-Pearson exact method for binomial data.

[a] Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

[b] Composite variable strategy: An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable.

without additional intervention. While the HBV functional cure outcome includes the loss of HBsAg, we chose a reduction of at least 1 log10 IU/mL in the qHBsAg level as a promising outcome measure at this developmental stage. Incremental changes and small effects from individual cure trials can lead to combination treatment trials that may lead to cure. For example, in the early days of hepatitis C virus (HCV) therapeutics, oral ribavirin monotherapy had a minimal impact on HCV RNA but in combination with interferon-alfa led to substantially higher cure rates (sustained virologic response). The A5394 study was designed to include placebo recipients, but the primary objective, qHBsAg decline, will be assessed as a single-arm evaluation in the participants receiving selgantolimod. The single-arm approach for the qHBsAg analysis was deemed appropriate because the chosen study population is not expected to achieve further qHBsAg reduction without an additional intervention. This has allowed for a small sample size in the trial. Inclusion of a small placebo group will facilitate innovative laboratory studies to be conducted as exploratory analyses with goals to characterize the mode of action of selgantolimod in the study population, and the blinding can help to reduce bias in safety assessments.

We concluded the description of A5394 with estimands to demonstrate the alignment of the objectives with the study elements, providing a streamlined snapshot of the study. Our approach highlights key considerations in trial design in the emerging field of HBV cure trials. Our decisions on the design elements were specific to the study agent, but our considerations may be informative for other early-phase HBV trials aimed at cure.

Funding source

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636 and UM1 AI106701. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Mark Sulkowski was partially supported by National Institute on Drug Abuse Midcareer Investigator Award in Patient-Oriented Research K24DA034621. Jennifer Price was partially supported by the AIDS Clinical Trials Group Clinical Trials Unit grant UM1 AI069496 from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Declaration of competing interest

The author authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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