# Protocol synopsis

**Title of study:**

A randomized open label study evaluating the efficacy of continued telbivudine versus lamivudine in patients with HBeAg-negative Chronic Hepatitis B who had previously achieved an undetectable viral load during 24 weeks of telbivudine therapy.

**Investigator**:

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**Purpose and rationale**:

The aim of this study is to investigate if a change of anti-viral therapy from telbivudine to lamivudine in patients who have achieved an undetectable viral load at week 24 of telbivudine therapy leads to more frequent viral breakthrough and more frequent selection of drug resistant viruses compared to continuous treatment with telbivudine.

**Objectives:**

The primary objective of the study is to assess the long-term efficacy of continued telbivudine therapy versus lamivudine switch in patients who previously achieved an undetectable viral load by TaqMan® PCR with telbivudine therapy at week 24.

The secondary objectives of the study are:

- To assess the rate of resistant mutations within the two treatment groups
- To assess the number of patients with a complete biochemical and virological response defined as negative HBV DNA and normal transaminases at week 48, 108, 156 and 204
- To characterize the mutations occurring during therapy
- To assess compliance with therapy
- To assess the safety of the treatments

**Population**:

This is a multinational multicenter study where the study population will be comprised of a total of 140 patients (70 patients in each group) with HBeAg-negative chronic hepatitis B.

**Inclusion/Exclusion criteria**:

- Male or female patients, $\geq$ 18 (having completed their 18$^{th}$ birthday). There is no upper limit of age
- Documented HBeAg negative CHB
- HBsAg positive $\geq$ 6 months
- HBV DNA > 2000 IU/mL
- Patient is willing and able to comply with the study drug regimen and all other study requirements.
- Written informed consent

- Anti-viral HBV treatment naïve or previous treatment with interferon-alpha or pegylated interferon-alpha stopped at least 1 month prior to screening

**Investigational and reference therapy**:

Run-in period: All patients fulfilling the inclusion criteria will be treated with telbivudine for 24 weeks.

Two-arm-treatment: patients with undetectable HBV DNA in the blood samples at week 24 will be randomized to either continue with telbivudine monotherapy (group A) or receive lamivudine monotherapy (Group B).

**Study design**:

This is a prospective, controlled, randomized, two-arm, open-label, multi-center, 4-year trial of telbivudine versus lamivudine in patients who previously achieved an undetectable viral load at week 24 of telbivudine treatment. Two interims analyses will be performed after week 108 and 156.

**Efficacy assessments**:

Serum HBV DNA determinations will be performed at the local laboratory through use of TaqMan®PCR method. Serum samples for HBV DNA will be obtained during Screening to determine eligibility for the study. The Screening serum HBV DNA values must be ≥ 2000 IU/mL by the TaqMan® PCR. Serum samples for HBV DNA will then be obtained every 12 weeks thereafter and at the End of Treatment visit if applicable. At week 24 patients must have undetectable HBV DNA values to be randomized. Undetectable HBV DNA is defined as HBV DNA values below the lower limit of detection (LOD) of the TaqMan® assay used by the local laboratories.

Patients with viral breakthrough (> 200 IU/mL) will have sequencing of their viral HBV isolates done in Lausanne (Laboratory of Prof. Dr. med. A. Telenti)

HBV serologic markers (HBsAg/Ab, HBeAg/Ab) will be assessed at the local laboratories using standard commercially available enzyme immunoassays.

Transaminase will be assessed throughout the study duration.

**Other assessments**:

- Assessment of adverse events including muscle symptoms
- Physical examinations, vital signs, height, weight, and pregnancy tests.
- Routine laboratory tests including biochemistry, prothrombin time, urinalysis.

**Data analysis**:
Data will be analyzed when all patients complete 108 weeks of study (first interim analysis), 156 weeks (second interim analysis) and complete Post-treatment Follow-up period (30 day follow-up after 204 weeks; final analysis). It is planned that data from all centers that participate in this protocol will be pooled, so that an adequate number of patients will be available for analysis.