A Multicenter, prospective, Non-Interventional Study Evaluating Response Parameters during and after Therapy with PEGASYS® (Peginterferon alfa-2a 40KD) in Subjects with HBeAg positive or HBeAg negative Chronic Hepatitis B

Short title: BENEFIT STUDY,

STUDY REPORT
(ML25614)

Synopsis/Abstract

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1 Abstract

1.1 Title
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1.2 Keywords
Hepatitis B; pegylated interferon; HBeAg; HBsAg; HBV-DNA

1.3 Rationale and background
Hepatitis B is one of the most frequent infectious diseases. As to secondary diseases possibly following chronic hepatitis B infection, it is assumed that worldwide 57% of all cases of liver cirrhosis and 53% of all cases of HCC are attributable to hepatitis B [2].

Treatment options of HBV infections are on the one hand administration of (pegylated) interferon alpha, on the other hand administration of nucleotide- or nucleoside analogues which inhibit the replication of HBV. Using interferon, a sustained therapeutical success can be achieved even when treatment is time-limited. [3].

Since the HBV cccDNA remains in the infected hepatocyte as a part of the genome and may be reactivated under certain conditions, healing as defined by eradication cannot be achieved. Because of the complex HBV replication and reproduction cycle, the therapeutic goal of PEGASYS® includes many intermediate steps: suppression of HBV replication, decrease of HBV-DNA titer, loss of HBeAg and seroconversion to anti-HBe in HBeAg positive virus carriers as well as loss of HBsAg and development of anti-HBs.

Accordingly, in the recent versions of the European and also of the German guidelines, the loss of or the seroconversion of the HBsAg respectively is regarded as the ideal therapeutic goal that is closest to healing of hepatitis B and corresponds to the status that is reached by patients after healing post acute hepatitis B infection [4].

1.4 Research question and objectives
Primary
• To assess in routine clinical practice the course of HBsAg and HBV-DNA during and after therapy in patients with HBeAg positive or negative chronic hepatitis B virus infection (CHB) being treated with PEGASYS® (Peginterferon alfa-2a 40KD) and followed for up to 2 years after treatment completion or cessation.
Secondary

- Evaluation of the incidence of sustained immune control (sustained suppression of HBV-DNA <2000 IU/ml in HBeAg negative and HBeAg positive patients or HBeAg seroconversion in HBeAg positive patients);
- Evaluation of the incidence of normalization of serum ALT;
- Evaluation of HBs Ag clearance and seroconversion;
- Evaluation of the incidence of clinical endpoints, where data available, in responders versus non-responders to treatment: death, transplantation, HCC, liver decompensation, development of cirrhosis (in patients without cirrhosis at baseline).

Safety and Tolerability

- Determination of safety and tolerability of chronic hepatitis B treatment with peginterferon alfa-2a (Pegasys®) in patients treated by gastroenterology specialists in a real-life setting. Additionally a descriptive alignment of the collected data with existing safety data and data from the approval trial of peginterferon alfa-2a (Pegasys®) to further establish the feasibility of the product in day-to-day practice was planned but not performed due to the premature termination of the study.

1.5 Study design
Non-interventional, multicenter, prospective

1.6 Setting
Physicians familiar with CHB treatment with pegylated interferon

Planned number of centers: 50
Actual number of centers: 17

1.7 Subjects and study size, including dropouts
Selected patient population: Adult subjects treated for CHB with PEGASYS® according to standard of care and in line with the current summary of product characteristics (SmPC)/local labeling who have no contraindication to PEGASYS® therapy as per the local label.

Selection criteria: Male and female subjects ≥18 years of age;
- HBeAg positive or HBeAg negative serologically proven chronic hepatitis B (CHB) with or without cirrhosis;
- Elevated serum ALT >ULN (upper limit of normal) but ≤10 × ULN according to local label;
- Subjects with no contraindications to PEGASYS® therapy as detailed in the label (Hypersensitivity to the active substance, to alpha interferons, or to any of the excipients; autoimmune hepatitis; severe hepatic dysfunction or decompensated cirrhosis of the liver; a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months);
- Subjects who are not co-infected with HAV, HCV or HIV;
Subjects should not receive concomitant therapy with telbivudine (because concomitant peginterferon therapy is contraindicated according to the telbivudine label);

Female subjects not pregnant or breast feeding when PEGASYS® treatment commenced, and aware of the requirement to use an effective method of contraception during therapy;

Written informed consent.

Planned number of patients: 250

Actual number of patients: 56 (no drop-outs)

1.8 Variables and data sources

Primary Variable:
- Changes in HBsAg (IU/ml) during therapy and follow-up
- Changes in HBV-DNA (IU/ml) during therapy and follow-up

Secondary Variables:
- In subjects with HBeAg positive CHB:
  - Percentage of subjects with suppression of HBV-DNA to <2,000 IU/mL during the observation period
  - HBeAg seroconversion defined as percentage of subjects who become HBeAg negative and anti-HBe positive during the observation period;
  - Percentage of subjects with HBeAg seroconversion and HBV-DNA suppression (<2,000 IU/mL) during the observation period;
  - Percentage of subjects with ALT normalization;
  - Percentage of subjects with HBsAg clearance/seroconversion (HBsAg negative, anti-HBs positive) during observation period.
- In subjects with HBeAg negative CHB:
  - Percentage of subjects with suppression of HBV-DNA to <2,000 IU/mL during the observation period;
  - Percentage of subjects with ALT normalization;
  - Percentage of subjects with HBsAg clearance/seroconversion (HBs Ag negative, anti-HBs positive) during observation period.

Other Variables of Interest for Subset of Subjects with available Data:
- Incidence of clinical endpoints associated with CHB reported in the medical record: Transplantation, HCC, liver decompensation, development of cirrhosis (in patients without cirrhosis at baseline) until 2 years post treatment
- Cause for mortality and reason for death recorded throughout the treatment and observational period
- All adverse events (serious and non-serious) were recorded during the treatment period

The observations and measurements to obtain the data to assess these variables are generally part of routine clinical practice in management of CHB treatment. Where data were available in the medical record, these were recorded in the eCRF.

1.9 Results

The study was prematurely terminated due to poor recruitment.

The results show a positive response to treatment with PEGASYS® in patients with chronic HBV hepatitis: HBsAg as well as HBV-DNA decreased during treatment, and the suppression of HBV-
DNA to values below 2,000 IU/mL and ALT normalization increased during therapy. However, clearance or seroconversion of HBsAg and seroconversion of HBeAg positive patients to HBeAg negativity and anti-HBe positivity and thus sustained immune control could not be shown. Concerning safety and tolerability of PEGASYS®, for 2 patients 1 SAE each was reported. Both SAEs were counted as “possibly related to PEGASYS® treatment”. 1 patient had to be withdrawn from treatment due to an adverse event (SAE: pregnancy) and for 1 patient PEGASYS® treatment was permanently discontinued because of an adverse event (SAE: gamma-glutamyltransferase increased). The intensities of 96.9% of all reported AEs were mild to moderate, for the remainder no intensity was recorded.

1.10 Discussion
The results show that the therapeutical goals of PEGASYS® treatment, suppression of HBV replication and decrease of HBV-DNA titer, can be reached under field conditions. In addition, all patients had an early (week 12 to 24) quantitative decrease of HBsAg compared to baseline, which is predictive for a sustained HBsAg clearance and virological response in HBeAg negative patients. For HBeAg positive patients it is known that a decrease of HBsAg corresponds with HBeAg seroconversion 24 weeks and 1 year after treatment.

As former experience and data showed that HBsAg and HBeAg seroconversion can be expected only within 1 year (HBeAg) or 3 to 5 years (HBsAg) after PEGASYS® treatment, it was obvious that seroconversion could not be shown in this study due to the premature termination and thus the limited data obtained.

But because of the poor recruitment and the premature termination of this study, the main goals, to capture the courses of HBsAg and HBV-DNA in a big patient population in a long-term setting and compare them to treatment response, could not be reached. Due to the few data, it could not be shown if any factors have predictive values concerning HBsAg seroconversion, control of the virus by the immune system and in the end treatment success.

Study data show no impact on the current risk profile of PEGASYS® as no SAEs were reported and also no unexpected AEs were reported. The frequencies of the reported AEs were within the known range as stated in the SmPC. As per SmPC, in clinical studies (treatment 48 weeks, follow-up 24 weeks) with patients suffering chronic hepatitis B adverse events occurred in 88% and serious adverse events in 6% of the patients and 5% of the patients had to be withdrawn due to adverse events. In the study concerned, the numbers are markedly lower with 40% adverse events, 0% serious adverse events and no withdrawals due to AEs.

All in all the data obtained are in line with the previous data and experiences about the efficacy and safety of PEGASYS®, but due to the few data and short observation time as result of the premature termination of the study the explanatory power of the study results is quite low.

1.11 Marketing Authorization Holder
Roche Pharma AG, Grenzach-Wyhlen