SCIENTIFIC DISCUSSION

1. Introduction

The hepatitis B virus (HBV) disease represents a major public health concern, with more than 350 million people infected and about 1 million deaths annually. The prevalence of HBV varies widely by geographic area, ranging from 0.1-2% in low prevalence areas such as Western Europe (primarily acquired through horizontal transmission during adulthood) to 8% and more in the high prevalence areas of South-East Asia and Sub-Saharan Africa (usually acquired through vertical transmission).

In Europe, the incidence of HBV infection is approaching 1 million, leading to 80 000 to 100 000 chronic HBV carriers, 19 000 cirrhosis and 5 000 HCC (Van Damne et al. Vaccine 1995; 13: 954-957). Incidence varies from 29 per 100 000 in Western Europe to 523 per 100 000 in Eastern Europe. The weighted average incidence for the WHO European region is 115 per 100 000 inhabitants. Hence, chronic hepatitis B is also a major public health concern in Europe.

HBV is a small DNA virus belonging to the hepadnaviridae family. The infectious enveloped particle has an outer protein coat (hepatitis B surface antigen or HBsAg) and an inner protein core (hepatitis B core antigen or HBcAg). In infected hepatocytes, HBcAg is produced in excess and during export from the hepatocytes is cleaved to release a hepatitis B e antigen (HBeAg). HBV has a high rate of spontaneous mutation. A mutation in the pre-core region of the gene coding for the nucleocapside stops the synthesis of the HBeAg. Such HBeAg negative or pre-core mutants patients, which account for 7 to 30 % of infections worldwide is particularly common in Southern Europe and Asia.

HBV infection is a complex disease that may either resolve spontaneously or manifest itself in variety of ways. Following acute hepatitis B infection, approximately 5% of adults and 20-90% of children, depending on the age at infection, fail to produce adequate immune response and become chronic carrier of the virus. Chronic carriers of HBV are at increased risk of developing long-term complications, i.e. cirrhosis, hepatic failure and hepatocellular carcinoma (HCC). Among patients with chronic active hepatitis B, some 40% will develop cirrhosis over their lifetime at a rate of approximately 2% per year. Among patients with compensated cirrhosis, 10% per year progress to a decompensated state, with a 1-year survival rate of 60%, compared with over 90% for compensated cirrhosis.

The ultimate goal of treatment of chronic hepatitis B is to suppress HBV replication and to induce remission in liver disease before cirrhosis and HCC develop. There are however remaining scientific uncertainties for instance which level of viraemia is associated with sustained virological response, with HBeAg seroconversion, whether viral clearance is an attainable goal because of the difficulty in eliminating the covalently closed circular form of HBV DNA (cccDNA) in the liver, when to stop safely the treatment (when viral eradication or when sustained suppression of viral replication necessary to prevent progression of disease are achieved).

There are currently four approved therapies for chronic HBV infection in Europe: alfa-interferon, lamivudine, adefovir dipivoxil, the prodrug of adefovir, and entecavir. Recombinant alfa-interferon acts primarily as an immunomodulator, whereas the nucleoside/nucleotide analogues directly inhibit viral replication. Current therapy of chronic hepatitis B has limited long-term efficacy and potential drawbacks. Therefore, there remains a great medical need for new therapeutic options for naïve patients as well as for patients with lamivudine-resistant HBV and for the more difficult to treat population (e.g. HBeAg negative patients, HIV co-infected patients and patients with decompensated hepatitis) with improved efficacy and safety profiles, with durable response and with low propensity for developing viral resistance.

The present application for marketing authorisation of Sebivo is made under Article 8.3 (i) and concerns a new active substance, telbivudine for which a complete dossier has been submitted. Telbivudine (LdT) is a thymidine nucleoside analogue of guanosine with selective activity against HBV.

The approved indication at the recommended dose of 600 mg once daily is: "for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. See section 5.1 *of the Summary of Product Characteristics* for details of the study and specific patient characteristics on which this indication is based."

2. Quality aspects

Introduction

Sebivo an immediate release dosage form is presented as film-coated tablets containing 600 mg of telbivudine as active substance. The other ingredients are cellulose microcrystalline, povidone, sodium starch glycolate, magnesium stearate, silicon dioxide and purified water. The film coat consists of hypromellose, talc, titanium dioxide, macrogol and purified water.
The film-coated tablets are marketed in PVC blisters lacquered to an aluminium foil.

Active Substance

The active substance is telbivudine and its chemical name is 1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione according to the IUPAC nomenclature.

Telbivudine is a white to slightly yellowish powder and only one crystalline form (form A) was identified. Telbivudine is sparingly soluble in water and aqueous solutions, soluble in methanol, very slightly soluble in ethanol, n-octanol and polyethylene glycol 400 and slightly soluble in propylene glycol, acetonitrile and cremophor EL/ethanol 65:35 (V/V). The above-mentioned active substance contains 3 chiral centres and is a single enantiomer (2S, 4R and 5S).

- **Manufacture**

Telbivudine is synthesised in three reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by recrystallisation.

Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, and mass spectroscopy. The molecular weight was determined by mass spectrometry. Elemental analysis is in agreement with the calculated composition.

- **Specification**

The active substance specifications include tests for appearance (white to slightly yellowish powder), particle size (laser light diffraction), identification (IR-KBr, IR-ATR and X-ray diffraction), impurities (HPLC), loss on drying (thermogravimetry), sulphated ash, specific optical rotation, heavy metals, clarity of solution, colour of solution, assay (HPLC), content of active substance and microbiological limit tests.

It was verified that all specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.

Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the

relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. The active substance is not susceptible to degradation under the influence of light, oxygen and nitrogen exposure. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the proposed retest period.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
Four strengths of Sebivo tablets were developed (25 mg, 100 mg, 200 mg and 600 mg) and used in clinical trials. However, only one tablet strength (600 mg) will be commercialised.
The main aim of the applicant was to develop a formulation that would rapidly release the active substance, for that reason different formulation containing different excipients were investigated and optimised.
Results of formulation and process development studies demonstrate that the tablet formulation and the manufacturing process are robust and under control.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, granulating, compressing and film-coating unit operations.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The medicinal product specifications were established according the ICH guidelines and include the following tests: appearance, identification (UV, HPLC and colour reaction), mean mass, dissolution after 30 minutes, impurities/degradants (HPLC), assay and microbial limits (Ph Eur).
All analytical procedures that were used for testing the medicinal product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
Batch analysis data on three stability batches and three production scale batches (validation batches) confirm satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. One production scale batch and two pilot scale batches have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch was stored under photostability stress testing under ICH conditions. The photostability results show that the tablets are not sensitive to light.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the Summary of Product Characteristics (SPC) are acceptable.

Overall information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

Introduction

Telbivudine (β-L-2′-Deoxythymidine, LdT) is the unmodified L-enantiomer of the naturally nucleoside D-thymidine. The non-clinical programme consisted of a series of studies aiming to define the pharmacological, pharmacokinetics and toxicological profile of telbivudine.
Safety pharmacology and toxicology studies were conducted in compliance with Good Laboratory Practices.

Pharmacology

- Primary pharmacodynamics

Telbivudine is phosphorylated to the monophosphate form, which is then sequentially converted to the 5′-diphosphate and to the active triphosphate form by cellular nucleoside kinases. Deoxycytidine kinase (dCK) and thymidine kinase (TK) are implicated in the conversion of telbivudine. Investigations suggested that telbivudine, in contrast to lamivudine, acts preferentially on HBV DNA second-strand synthesis (DNA-dependent DNA synthesis) rather than first minus DNA strand synthesis (reverse transcription). It is not clear how this feature translates into clinical activity.

Telbivudine is phosphorylated in a dose-dependent manner in hepatoma cells and primary hepatocytes. Telbivudine tri-phosphate inhibits hepadnaviral DNA synthesis with an inhibitory concentration (IC_{50}) for virion-associated woodchuck hepatitis virus (WHV) polymerase of 0.24 μM.

In hepatoma cell culture assays (2.2.15 cells derived from HepG2 cells), telbivudine inhibited HBV production with a mean 50% effective concentration (**(**EC_{50}) of 0.19+/-0.09 μM. Viral rebound occurred after treatment withdrawal and HBV replication returned to 50% of pre-treatment levels by day 10 post-treatment. The kinetics of viral rebound suggested that the antiviral effect seen after withdrawal was consistent with the intracellular half-life of 14 hours in HepG2 cells.

Telbivudine was non-cytotoxic to the human hepatoma cell line 2.2.15: 50% cytotoxic concentration (CC50) > 2000 μM. Telbivudine was not cytotoxic to human peripheral blood mononuclear cells (CC50 > 200 μM).
In in-vitro studies telbivudine-TP was not an inhibitor of human DNA polymerases α, β, or γ at concentrations up to 100 μM, the highest concentration tested.

The antiviral activity of telbivudine against lamivudine or adefovir resistant HBV genomes has been extensively evaluated.
The genotypic identities of the HBV genomes in the cell lines tested were the lamivudine selected mutations M204V, M204I, L180M + M204V, L180M + M204I in comparison with wild-type.
Telbivudine was essentially inactive (EC_{50} > 1000 μM) against the M204I or the L180M/M204V mutant viruses. Telbivudine reached an EC_{50} below 1000 μM against L180M/M204I double mutant in some but not all experiments. However, telbivudine exhibited essentially unchanged anti-viral activity against the M204V mutant virus.
Like lamivudine, telbivudine is active in cell lines against the N236T mutant, which so far seems the primary mutation responsible for resistance to adefovir dipivoxil.
In vitro, cross-resistant data showed that the second conserved site mutation rtA181V which conferred clinical resistance to adefovir dipivoxil led to only a modest reduction in the activity of telbivudine (3.7 fold).

Overall results suggest that telbivudine is cross-resistant with lamivudine and entecavir.

In vivo studies were conducted in woodchucks, species that is susceptible to infection with hepatitis virus. In a 28-day study, telbivudine was active at all doses tested (0, 0.01, 0.1, 1.0 and 10 mg/kg/day given orally once daily). Telbivudine showed a clear dose response at the end of treatment. Serum WHV DNA levels decreased by up to 8 log10 and to below the limit of detection by PCR in two of the dosed animals and by about 6 log10 in the third animal. Following treatment withdrawal at day 28, viral rebound reached near pre-treatment levels between weeks 8 and 12 (day 56 and 84).
In the other study, after 12 weeks of telbivudine at 1 mg/kg/day the decline in serum WHV DNA was more gradual. Individual animals showed more variation in the extent and duration of antiviral suppression. Nevertheless, WHV viral load reductions of at least 6 to 7 log10 were seen in the four telbivudine-treated animals at some point during therapy. Serum WHsAg levels decreased throughout the treatment phase by 0.5 to 1.5 log10 from baseline and WHsAg rebound lagged behind viral load rebound by approximately 1-2 weeks. All were positive for WHV core antibody and there was no evidence of an anti-WHsAg response during the 12-week follow-up.

Unlike lamivudine and adefovir but like entecavir, telbivudine did not inhibit replication of any other virus than hepadnaviruses including HIV.

- Secondary pharmacodynamics

The absence of specific secondary pharmacodynamics studies is acceptable taking into consideration the specificity of telbivudine against hepadnaviruses, the absence of inhibition of human DNA polymerases α, β and γ by telbivudine -TP, the lack of mitochondrial toxicity of telbivudine *in vitro* and the weak cytotoxicity of telbivudine against various human cell lines.

- Safety pharmacology programme

Safety pharmacology studies investigated the effect of telbivudine on cardiovascular, respiratory and central nervous systems. Cardiovascular and respiratory endpoints were examined in cynomolgus monkeys after single oral doses up to 2000 mg/kg. Toxicokinetic data suggested that this dose would have produced an exposure (AUC_{0-24}) of approximately 9 times the expected human exposure following a 600 mg/day dose. No effects on cardiovascular or respiratory variables were seen.
Telbivudine did not show any potential for QT interval prolongation, as it had no effect on potassium channel (hERG) current at concentrations up to 10,000 µM.
Effects on the central nervous system were assessed by means of a functional observational battery in rats. Single oral doses up to 1000mg/kg did not cause any adverse clinical signs. Toxicokinetic data suggested that this dose would have produced exposure (AUC) of approximately 7 times the expected human exposure.
The lack of safety pharmacology studies on renal and gastrointestinal systems was considered acceptable in view of the lack of findings on these systems reported in the general toxicity studies as well as in the clinical development.

- Pharmacodynamic drug interactions

No antagonistic antiviral activity was evidenced *in vitro* between telbivudine and NRTIs active against HIV.

Pharmacokinetics

Pharmacokinetic characteristics of telbivudine were studied in the species used in toxicological studies (mice, rats, rabbits, and monkeys) as well in pharmacodynamic studies (woodchucks). Telbivudine plasma concentrations were measured using sensitive and specific HPLC with UV detection and/or LC-MS/MS methods.

- Absorption- Bioavailability

Telbivudine was absorbed at a moderate to fast rate (Tmax 0.5-3.0 hr). The oral bioavailability of telbivudine (10 mg/kg) was 60% in rats, 59% in monkeys and 38% in woodchucks. Studies conducted with fed and fasted female rats suggested that food had no effect on the absorption of telbivudine (10 mg/kg dose).
Telbivudine exposure was less than dose-proportional especially at doses greater than 1000 mg/kg. As shown by an in vitro Caco-2 study, telbivudine has moderate permeability properties. Various in vitro studies demonstrated that telbivudine does not interact with P-gp and MRP. A lack of interaction between telbivudine and transporters was also shown in humans.
There were no sex-related differences in the pharmacokinetics profile of telbivudine.

- Distribution

Following oral administration (10 mg/kg) of [^{14}C]-telbivudine to male rats, telbivudine was widely distributed, with the highest concentrations observed in small and large intestines, urinary bladder, kidneys, prostate gland, mesenteric lymph nodes, stomach, and pancreas. There was limited penetration to the central nervous system, moderate crossing the placenta, and substantial secretion into rat milk as evidenced by a milk/plasma AUC ratio of 2.3.
Telbivudine was weakly bound to plasma protein (from 3.3 to 7.5% in rat, monkey and human) and was independent of telbivudine concentration over the range evaluated (0.4 to 40 µg/ml). Telbivudine partitioned into the erythrocytes of rats, monkeys and humans independently of its concentration (range 32 to 43%).

- Metabolism and elimination

Telbivudine undergoes extensive in vitro anabolism to form the 5'-mono-, the 5'-di-, and the 5'-tri-phosphate derivatives, the later moiety being the active form of telbivudine.

While the mono-, di- and triphosphate metabolites of telbivudine have been observed *in vitro*, they have not been seen in plasma, urine or faeces *in vivo*. Following a single oral dose of radiolabelled telbivudine to rats, the parent compound was the predominant radioactive component excreted in both males and females. One minor and unidentified metabolite (M-4) was observed in females. This metabolite represented up to 3.9% of the radioactivity present in plasma and no more than 7.3% of radioactivity in urine (representing no more than 1.1% of the administered radioactivity). Analysis of the bile revealed five compound derived peaks including M-4. As less than 0.80% of the total administered dose was eliminated in the bile, these were considered to be minor metabolites.
No metabolites were observed in plasma or urine of monkeys or woodchucks receiving radiolabelled telbivudine.

After a single oral administration of [^{14}C]-telbivudine to rats (10 mg/kg) radiocarbon was eliminated in both urine and feces in approximately equivalent amounts (40-50%) over 168 hr; overall recovery of radiocarbon was >91%. The comparison of results after both routes of administration suggested that urine was the primary route of excretion, and that radioactivity recovered in the feces after oral administration corresponded to unabsorbed substance.

In monkeys, drug-related radioactivity was primarily eliminated in the urine following intravenous administration of [^{3}H]-telbivudine (74% of the dose as telbivudine). After oral administration, 36.6% of the administered compound was eliminated in the urine.

Telbivudine was eliminated at a moderate to rapid rate (t1/2 2-8 hr) in mice, rats, and woodchucks, but more slowly in monkeys (t1/2 7.5-18 hr) and humans (t1/2 41.1 hr). No gender differences were observed in elimination.

Telbivudine did not inhibit *in vitro* human CYP450 enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. In addition, Telbivudine did not induce rat CYP1A2, CYP2B, 3A or 4A *in vivo*. The occurrence interactions with other compounds mediated via cytochrome P450 therefore seems unlikely.

Toxicology

A comprehensive toxicological programme was conducted in mice, rats, and monkeys.

- Single dose toxicity

In rats and monkeys, telbivudine did not show any clear signs of toxicity at oral doses up to 2000 mg/kg.

- Repeat dose toxicity (with toxicokinetics)

Studies were conducted in mice up to 13 weeks, in rats up to 6 months, and in monkeys up to 9 months.
After oral administration in mice, telbivudine did not induce particular signs of toxicity. Therefore, it was concluded that in both 4- and 13-weeks studies the high-dose levels (2000 mg/kg/day and 3000 mg/kg/day respectively) were the no-observed adverse effects (NOAEL), corresponding to animal exposures of at least 22-times the anticipated human exposure.

Telbivudine administered orally to rats for 28 days and 6 months did not reveal histological evidence of toxicity. As in mice, it was concluded that the high-dose levels administered were the NOAELs (2000 mg/kg/d and 1000 mg/kg/d respectively). Toxicokinetic data indicated that exposures of animals at these NOAELs (in terms of AUC) were 14 and 6 times the anticipated human exposure respectively.
An intravenous dosing study in rats was associated with changes in the kidney, pancreas and heart. While exposure, in terms of AUC, was greater in the oral dosing study the Cmax seen following administration of the high intravenous dose was greater than that seen following administration of the high oral dose. This may suggest that the histological evidence of toxicity seen in the intravenous dosing study was related to the rate of infusion.

In monkeys, high oral doses of telbivudine (≥ 1000 mg/kg/day) caused some gastro-intestinal intolerance, as evidenced by occasional soft stools and emesis. In the 9-month study, equivocal evidence of axonopathy was seen at the highest dose tested (1000 mg/kg/day). A re-analysis showed that effect on sciatic nerves was most evident in high dose female group, while the effect on spinal cord was most evident in high dose male group. A possible effect of telbivudine could not be ruled out. In this study the NOAEL was therefore considered to be 500 mg/kg/day corresponding to an animal/human exposure multiple of 4.5.

Overall while repeat oral dosing studies revealed little toxicity, the ratio animal/human exposure were modest. Nonetheless at high doses, toxicokinetic results showed a non-linear relationship between the dose and the exposure suggesting that it would have been difficult to obtain animal exposures higher than the ones obtained in the studies conducted by the applicant.

- Genotoxicity

In the standard battery of tests, telbivudine was not clastogenic or mutagenic *in vitro*. Also, there was no evidence for genotoxic potential *in vivo* in the mouse micronucleus test (concentrations up to 2000mg/kg).

- Carcinogenicity

The carcinogenic potential of telbivudine was assessed in rats and in the mice Tgras H2 transgenic model. Due to low survival rates, especially in rats receiving the high dose (38% at 2000 mg/kg/day), the originally planned duration was shortened from 104 weeks to 85 weeks (high dose group) or 95 weeks (control, low dose and mid dose groups). It is not clear if the maximum tolerated dose was achieved however administrating a higher dose of telbivudine would probably not have resulted in a significant higher exposure. The study suggested that telbivudine might have contributed to the progression of chronic progressive nephropathy, particularly in the mid and high dose groups but as chronic progressive nephropathy is not considered to have a correlate in humans, this finding was considered of limited significance. While there was an increased incidence of certain neoplasms (pancreatic acinar cell adenomas, benign phaeochromocytoma of the adrenal medulla and fibroadenoma of the mammary gland), particularly in high dose group, the size of the effects and the lack of a dose response relationship suggests that these findings may have been incidental.

In the 26 week oral dosing study in TgrasH2 transgenic mice, telbivudine did not show any carcinogenic potential and the NOAEL was 2000 mg/kg/day, the highest dose tested.

- Reproduction Toxicity

In the combined fertility and developmental toxicity study in rats, a lower fertility rate was noted in pairs given 500 mg/kg/day (76%) or 1000 mg/kg/day (72%) when compared to controls (92%). Oral doses up to 1000 mg/kg/day of telbivudine did not cause adverse effects on foetal development Fertility was further investigated in separate studies in male and female rats at dosages up to 2000 mg/kg/day and no effects on fertility nor on general reproductive function were observed.

In the embryo-foetal development toxicity study in rabbits, reduced body weight gain and reduced food consumption were observed in the high oral dose group (1000 mg/kg). Increased incidence of abortion and early delivery observed for the high dose was secondary to maternal toxicity. There were no developmental anomalies detected. NOAEL maternal was 250 mg/kg/day and NOAEL developmental was 1000 mg/kg for foetal effects corresponding to 37 times the human dose based on AUCs obtained in pregnant rabbits.

The perinatal and postnatal development study in rats with doses up to 1000 mg/kg did not show any adverse toxic effects with telbivudine.

The absence of studies in juvenile animal was considered acceptable as telbivudine is not indicated in children.

- Local tolerance

There were no specific studies assessing the local tolerance as telbivudine is to be administered orally. While inflammation was noted at the injection site in the intravenous toxicity study, it was attributed to repeated injections rather than irritation due to telbivudine.

- Other toxicity studies

Telbivudine did show any evidence of mitochondrial toxicity in a model (HepG2) currently used for this type of study. In addition a study for up to 12 weeks in woodchucks, a species reported to be sensitive indicator of mitochondrial toxicity, did not reveal signs of potential mitochondrial toxicant for telbivudine.

As certain nucleoside analogues have myelosuppressive effects (eg anemia, neutropenia) the effect of telbivudine on human bone marrow progenitor cell colony formation was examined but no effect on hematopoietic progenitor cells was observed.

The potential of telbivudine to induce contact allergy was assessed in a GLP study using the murine local lymph node assay. Telbivudine did not produce immune system activation.

No studies to evaluate the toxicity of metabolites have been performed considering the lack of telbivudine metabolites detected in humans and of no major metabolites detected in plasma of rats, woodchucks or monkeys.

There were no impurities that required toxicological qualification.

Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) was 0.3 µg/l, which exceeds the trigger value (0.01 µg/l). Therefore, a phase II assessment was deemed necessary.

Parameters calculated in the phase II assessment

PNECsurfacewater	94.9 ng/l
PNECmicroorg	3 mg/l
Refined PECsurfacewater	1.5 ng/l
PEC microorg	15 ng/l

The applicant conducted also a brief groundwater risk assessment. Telbivudine is unlikely to persist in the environment. These data taken together indicate a low environmental risk for telbivudine.

4. Clinical aspects

Introduction

The clinical programme, mainly conducted in Asia, consisted of:

- studies aiming to characterise the pharmacokinetics profile of telbivudine (including interaction studies, studies in special populations and population PK analysis),
- dose finding trials (Phase I/IIa study: NV-02B-001 and international Phase IIb trial: NV-02B-003 and its extension phase NV-02B-010),
- a global Phase III (NV-02B-007 also called Globe) comparing the efficacy and safety of telbivudine versus lamivudine in a mixed population of HBeAg positive and negative, nucleoside/nucleotide naïve adult patients with compensated chronic liver disease.

Good Clinical Practices

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.
An inspection was conducted at the EMEA request to assess the GCP standards in investigator sites in Thailand and China of the pivotal study NV-02B-007. The standard of GCP compliance at both sites in this trial was found to be equivalent to EU standards.

Pharmacokinetics

The pharmacokinetics of telbivudine has been evaluated using validating methods in 15 Phase I studies in healthy volunteers or special populations and one Phase I/IIa in HBV infected patients, as well as in a population pharmacokinetic analysis using the results from all Phase I/II studies. The pharmacokinetics of telbivudine in HBV infected patients has not been evaluated with the recommended dose of 600 mg.

- Absorption

Telbivudine was rapidly absorbed following single oral administration (600 mg) with Tmax attained in 3h (1 – 6), a Cmax of 3.2 ± 1.1mg/l, AUCo-t of 28.0 ± 8.5 mg.h/l and AUCo-inf 30.0 ± 8.7 mg.h/l.
Due to the lack of an adequate intravenous formulation, the oral absolute bioavailability has not been determined. The bioavailability has nonetheless been estimated to be about 42 %.

Bioequivalence between the clinical trial tablet formulations and the film-coated tablet to be marketed was demonstrated.

There was no food effect on telbivudine bioavailability and therefore as recommended in the Summary of Product Characteristics, telbivudine can be taken with or without food.

- Distribution

Due to the lack of intravenous formulation, the apparent volume of distribution has not been determined but estimated to be 8.2 $\pm$ 4.1 l/kg, suggesting that telbivudine widely distributed into tissues. Protein binding was low (between 2 – 5 %) and constant over the range of therapeutic concentrations. Telbivudine equally partitioned between plasma and blood cells in a concentration independent manner with a mean erythrocyte-to-plasma concentration ratio of 1.01.

- Elimination

Plasma telbivudine penetrated into the hepatocytes and was converted to mono, di - and tri-phosphorylated metabolite. The 5-triphosphate derivate was the predominant active metabolite. The in vitro intracellular half-life of telbivudine 5'triphosphate was approximately 14 hours in liver cells. Other than intracellular conversion to its active 5'-triphosphate derivative (found *in vitro*), telbivudine did not appear to undergo detectable metabolism *in vivo*.

The mass balance study showed that 42 % and 49.6 % of 14C labelled telbivudine single oral dose (600 mg) was recovered in urine and faeces respectively (total 91.6 %). No metabolites were found in plasma, urine or faeces. Renal clearance (130 ml/min) approached total clearance indicating that renal route was the major elimination pathway mainly by glomerular filtration.

The plasma decay of telbivudine was biexponential with a short T½ of approximately 3 – 5 h followed by a second slower elimination phase of 40 – 50 h which was evidenced by sampling up to 16 h.

In vivo interconversion of telbivudine to the endogenous β-D-thymidine has been shown to be unlikely.

- Dose proportionality and time dependencies

Dose proportionality of telbivudine was shown for Cmax and AUCo-t over a dose range of 25 to 1800 mg although in some Chinese and Japanese PK studies, the PK of telbivudine appeared to be less than dose-proportional in the upper range of the tested doses.

Following multiple doses administration, steady-state was reached within 5 to 7 days. The mean value of terminal half-life after repeated administration was similar to that after single dose suggesting that the systemic clearance did not change after multiple dosing.
The mean accumulation ratios were low i.e. 1 – 1.2 for Cmax and 1.2 – 1.5 for AUC.

The inter-individual variability for Cmax and AUC of telbivudine was moderate around 30 % while the intra-individual variability was lower (10-20%).

- Special populations

Renal impairment

The effect of renal impairment on the pharmacokinetics of telbivudine was assessed in a single dose study where subjects were assigned to the following doses administered on Day 1 depending of their degree of impairment: 600 mg (normal and mild impairment), 400 mg (moderate impairment), 200 mg (severe impairment), 200 mg either 2 hours before or within 2 hours after hemodialysis and opposite schedule on Day 8 (end stage renal disease).

In subjects with moderate renal impairment (Clcreat 49 – 30 ml/min), the 600 mg normalized AUC0-48 h was equivalent to 2 x AUC0-24 h from the normal group. In subjects with severe renal impairment (Clcreat < 30 ml/min) the 600 mg normalized extrapolated AUC0-72 h was approximately equivalent to 3 x AUC0-24 h from the normal group and in subjects with end stage renal disease (hemodialysis) the 600 mg normalized extrapolated AUC0-96 h was 4 x AUC0-24 h the normal subjects.

Based on the results on dose-normalized telbivudine parameters of exposure, and pharmacodynamic considerations, dose adjustment through extending dosing interval of the recommended 600 mg dose was proposed i.e 600 mg once every 48 hours (Clcreat 30 – 49 ml/min), 600 mg every 72 hours (Clcreat <30 ml/min not requiring dialysis) and 600 mg once every 96 hours (ESRD). However these recommendations are not based on results from patients with impaired renal impairment receiving 600 mg dose. A warning has therefore been introduced in the SPC highlighting that the dose interval adjustment might lead to sub-optimal exposure in some patient and requiring close monitoring of virological response. In addition applicant committed to explore with an oral solution under development possible daily dose adjustment in patients with renal impairment.

Hepatic impairment
A parallel group study was conducted in 24 patients with normal or impaired hepatic function [Child Pugh scores of 5-6 (mild), 7-9 (moderate) and 10-15 (severe)] to assess the impact of hepatic impairment on the pharmacokinetics of telbivudine after oral administration of a single 600 mg dose.
Results showed that the median Cmax and AUC values in subjects with mild, moderate and severe hepatic impairment were close to normal subjects. However there were three outliers identified (one per hepatic impairment group) on the basis of the criteria in the protocol with AUC value much higher to other patients. Further analysis showed that the increased exposure and decreased clearance seen in those "outliers" were reflective of impaired renal function that is often associated with hepatic dysfunction. On the basis of these results, no dose adjustment is recommended in patients with hepatic impairment if they present adequate renal function. More information will be obtained post-authorisation from an ongoing phase III trial (Study NV-02B-011) in HBV-infected patients with decompensated liver diseases**.**

Gender, weight, age, race
Gender did not affect telbivudine pharmacokinetics, which was confirmed in the population PK.

The effect of weight was not specifically investigated. In the population PK analysis, weight was not identified as a covariate influencing telbivudine clearance.

Pharmacokinetic studies have not been conducted in elderly. Some data included from the population PK analysis suggest that age was not a covariate of PK parameters of telbivudine PK (19-76 years).

No conventional pharmacokinetic study was designed to investigate the effect of ethnic origin in the pharmacokinetics of telbivudine. The population pharmacokinetic analysis identified that the race had an effect on exposure (~ 20 % decrease in telbivudine exposure in Hispanic versus Caucasians, Africans, Chinese and Japanese ethnic groups) but this was considered not clinically relevant.

Paediatric population
There are currently no pharmacokinetic data in children or adolescents.

Pharmacokinetics in target population
Pharmacokinetics of telbivudine in patients with chronic hepatitis B were assessed after repeated administrations of daily doses ranging from 25 to 400 mg and 800 mg. Based on the data available, the pharmacokinetics in HBV infected patients appears similar to that in healthy volunteers. Nevertheless further data on pharmacokinetics in HBV HBeAg positive infected patients receiving the recommended 600 mg dose will be provided post-authorisation.

- Pharmacokinetic interaction studies

Based on the pharmacokinetic properties of telbivudine showing that elimination through metabolism is limited and that the main pathway of elimination as unchanged is via the kidney, a caution has been included in the SPC on the potential co-administration with other substances that may affect renal function. In addition studies in healthy volunteers were performed to establish whether telbivudine could interact either with other antivirals which share the same pathway of elimination or that could be co-administered with telbivudine in hepatitis B treatment. In addition, a study was performed to evidence any interaction between the immunosuppressive agent cyclosporin administered in transplant recipients and telbivudine.

Co-administration of telbivudine (200 mg daily) with lamivudine (100 mg daily) increased the Cmax telbivudine with a ratio of 107 (90% CIs 89-129). The ratio for AUC was 106 (90% CIs 92-123). Lamivudine Cmax decreased on co-administration (ratio 86, 90% CIs 71-104) while AUC was unaffected (ratio 99, 90% CIs 87-112). Although the study did not reveal any clinically relevant interaction, there is no information at a clinical dose of telbivudine.

In the telbivudine/pegylated interferon study, while the telbivudine PK 600 mg (as 3 x 200 mg tablets) was not affect by concomitant pegylated interferon alfa 2a (single dose 180 µg), the 90% CI for the Peg-IFN parameters, though containing 100%, fell outside the pre-defined 80-125% range for

equivalence, likely due to the larger than anticipated inter-individual variability of Peg-IFN parameters (CV%: ~70% for C_{max} and AUC) and small sample size in this study. Although the AUC and C_{max} of Peg-IFN in combination with telbivudine were comparable to historical data (Modi et al 2000), the high inter-individual variability of the pegylated interferon pharmacokinetics makes it difficult to draw definitive conclusion in this field. Further interaction data derived from the clinical study investigating this combination therapy will be provided post-authorisation.

Co-administration of multi doses of telbivudine (600 mg) and adefovir dipivoxil (10mg) did not affect the PK of either compound: the 90% CIs for C_{max} and AUC, for all studied agents were within the 80% to 125% target range.

The steady-state pharmacokinetics of telbivudine and cyclosporin A appeared to be unaltered following multiple dose administration of telbivudine in combination with multiple doses of cyclosporine A (4 mg/kg/day given in two divided doses). The mean peak and AUC whole blood cyclosporin values were higher on co-administration with telbivudine and the 90% CIs for the comparison of Cmax were 106-126. Nevertheless, given the potential toxicity of telbivudine and cyclosporin on the muscle a pharmacodynamic interaction cannot be excluded. A warning has therefore been included in the SPC.

Preliminary results of a study between telbivudine and tenofovir did not reveal any potential interaction. The final results will be provided as part of the follow-up measures to be fulfilled post-authorisation.

There was no interaction between telbivudine (3 x 200 mg tablets) with an experimental nucleoside compound valtorcitabine (2 x 300 mg tablets).

Pharmacodynamics

- Mechanism of action

As already mentioned in section 3.3, telbivudine is a selective inhibitor of HBV replication.

Telbivudine resistance profile:

Evidence of telbivudine resistance was firstly described in vitro studies and in clinical study NV-02B-003 where M204I mutation was identified as the key determinant behind telbivudine resistance.

A genotypic analysis was performed based on the sequencing and genotyping of virus sample in all patients included in pivotal phase III study NV-02B-007 (described under the main study) and the sequencing of the virologic breakthrough patients identified in the study.
Virologic breakthrough and treatment-emergent HBV resistance was significantly lower for telbivudine recipients compared to lamivudine recipients in both the HBeAg-positive and HBeAg-negative patient populations (table 1).

Table 1 Virologic Breakthrough and Treatment-Emergent HBV Resistance at Week 48, by HBeAg status – ITT population

	HBeAg-positive			**HBeAg-negative**		
	Lamivudine	Telbivudine	p-value	Lamivudine	Telbivudine	p-value
	N=442	N=438		N=187	N=192	
Endpoint	n (%)	n (%)		n (%)	n (%)	
Virologic Breakthrough	46 (10.4)	15 (3.4)	<0.0001	16 (8.5)	4 (2.1)	0.0052
HBV Resistance	36 (8.2)	13 (3.0)	0.0007	16 (8.5)	4 (2.1)	0.0052

However, there was a concern about the definition of virologic breakthrough used to detect rebound (based on either a confirmed HBV DNA> 5 log10 copies/ml or a $\geq$ 1 log10 copies/ml increase according to the initial virologic response) which may have led to underestimate the emergence of resistance.

The applicant re-analysed the data using a revised definition of virologic breakthrough, as confirmed ≥ 1 log10 copies/ml increase in HBV DNA from nadir by PCR assay. Results of the new analysis shown in table 2 did not modify the study conclusions from the original analysis.

Table 2: Virologic Breakthrough and Treatment-Emergent HBV Resistance at Week 48, by HBeAg status – ITT population

	HBeAg-positive			HBeAg-negative		
	Lamivudine N=463	Telbivudine N=458	p-value[3]	Lamivudine N=224	Telbivudine N=222	p-value[3]
Endpoint	n (%)	n (%)		n (%)	n (%)	
Virologic Breakthrough	71 (15.3)	27 (5.9)	<0.0001	28 (12.5)	5 (2.3)	<0.0001
HBV Resistance[2]	51 (11.1)	23 (5.0)	0.0006	25 (11.2)	5 (2.3)	0.0001
Sequencing Not Done	5	0		0	0	

[1]In patients with a confirmed 1 $\log_{10}$ copies/ml decrease in HBV DNA from Baseline, Virologic Breakthrough defined as a confirmed ≥ 1 $\log_{10}$ copies/ml increase from nadir by PCR assay.

[2]Results exclude breakthrough patients who have not been sequenced.

[3]P-values for difference between proportions controlling for randomisation strata.

The applicant provided also the results of a resistance analysis based on patients without virological breakthrough but with detectable HBV DNA levels at Week 52. In this analysis an approximately 10% rate of emergence of resistance was observed at one year with no new mutation apart from the M204I.

Analysis of resistance at 104 weeks

The completed analysis of the final 2 years resistance data for NV 2B-007 is not yet available but the applicant provided a preliminary analysis of resistance at Year 2 using August 23, 2006 as the cut off date (table 3). This analysis took the patients selected from the unlocked database (as meeting the relevant breakthrough criteria) and focused exclusively on examination of mutational changes at codon M204.

Table 3: Preliminary Resistance (Viral Breakthrough with M204 mutation) Summary at Year Two

	HBeAg Positive		HBeAg Negative	
Analytic Method	LdT	Lam	LdT	Lam
Per protocol[1]	17.8%	30.1%	7.3%	16.6%
1 log above nadir[2]	21.6%	35.0%	8.6%	21.9%

[1]HBV DNA returns to > 5 $\log_{10}$ copies/ml or within 1 $\log_{10}$ copies/ml of baseline and with M204 resistance mutation
[2]HBV DNA returns to 1 $\log_{10}$ copies/ml above nadir and with M204 resistance mutation

The resistance rates increased for both lamivudine and telbivudine treatment groups during the second year of treatment although there was a slightly lower resistance rate with telbivudine.

The applicant committed to provide further data on resistance, including cross-resistance, as part of the follow-up measures to be fulfilled post-authorisation.

- Relationship between plasma concentration and effects

An analysis performed in study NV02B-001 regarding plasma concentrations and effects on plasma HBVDNA. This is presented under the dose selection study section.

A clinical pharmacology study (NV-02B-024) evaluated the effects of telbivudine on cardiac safety. In this placebo-controlled study, the effect of telbivudine on cardiac repolarization (QT/QTc interval duration) in healthy volunteers was evaluated at clinical (600 mg/day) and supra-therapeutic (1800 mg/day) telbivudine doses. No safety concerns have been identified.

Clinical efficacy

The clinical dossier consists of efficacy/safety data derived from a limited number of studies only performed in nucleoside/nucleotide naïve adult patients with compensated liver disease and mainly conducted in Asia. An overview of these studies is presented in table 4.

Table 4 Overview of the clinical trials

Study Design	Study Number	Details
Dose-finding trials	**NV-02B-001**	Phase I/II, randomised, blinded, controlled
	NV-02B-003	Phase IIb, randomised, blinded, controlled, dose-confirmation and preliminary efficacy trial
Controlled trials	**NV-02B-007**	Large, randomised, double-blind, Phase III trial comparing telbivudine with lamivudine
Long-term data	**NV-02B-010**	Extension to NV-02B-003
	NV-02B-007	Week 76 data and preliminary 104 weeks

Dose selection studies:

The telbivudine dose selection was based on the results of 2 studies:

- a Phase I/II dose-escalation study NV-02B-001 investigating the telbivudine doses over the range of 25 mg to 800 mg daily
- a one-year Phase IIb dose-confirmation study NV-02B-003 that examined two doses of telbivudine 400 mg and 600 mg alone or in combination with lamivudine. There was two-year extension study of NV-02B-003 [study NV-02B-010].

Both studies were performed in HBeAg positive patients with no prior nucleosi/tide therapy.

Study NV-2B-001

Telbivudine was associated with marked anti-HBV activity. A virological response (≥ 2 log10 decrease from baseline in HBV DNA at Week 4) was obtained in 34/35 [97%] telbivudine-treated patients compared to none on placebo. The median and mean reductions in HBV DNA over time showed a trend to increase with dose and were typically maximal at the end of treatment (Week 4), when median reductions (in log 10 copies/ml) were 2.50 in the 25 mg group, 2.68 for 50 mg, 3.19 for 100 mg, 2.89 for 200 mg, 3.63 for 400 mg and 3.75 for 800 mg. In contrast, the median reduction in the placebo cohort was 0.13 log10 copies/ml.

The relationship between telbivudine dose and HBV DNA reduction was examined by an Emax modelling approach. Telbivudine exhibited a quantitative exposure-viral response relationship with about 3 log10 copies/ml reduction in serum HBV DNA at week 4 at the 200 mg/day dose and near maximum antiviral effects (3.5-4.0 log10 copies/ml reduction in viral load) achieved with telbivudine doses of 400-800 mg/day.

Study NV-02B-003

The antiviral effects of five oral antiviral treatment regimens were investigated:
Group A: LdT-400 (telbivudine 400 mg/day).
Group B: LdT-600 (telbivudine 600 mg/day).
Group C: LAM-100 (lamivudine 100 mg/day).
Group D: LdT-400/LAM-100 (telbivudine 400 mg and lamivudine 100 mg/day).
Group E: LdT-600/LAM-100 (telbivudine 600 mg and lamivudine 100 mg/day).

This study enrolled 107 patients, predominantly Asian (86%), males (81 %) with a mean age of 37 years. The primary efficacy endpoint was HBV DNA area-under-the-curve (AUC) from Week 1 to Week 12, termed HBV DNA AUCMB (Weeks 1-12), expressed in log10 copies/ml, with the primary comparison being the results for the pooled 400 mg/day telbivudine dosing groups (Groups A and D) vs. the pooled 600 mg /day dosing groups (Groups B and E).

Results on the primary efficacy endpoint, change in HBV DNA levels from week 1 to week 12 (AUCMB 1-12) are presented in table 5.

Table 5: HBV DNA (log10 copies/ml) normalized AUCMB values and changes from baseline (week 0) or week 1 at selected visits through week 52 by individual treatment group (ITT population)

	LAM-100	LdT-400	LdT-600	LdT-400/ LAM-100	LdT-600/ LAM-100
HBV DNA (log10 copies/ml)	**(N=19)**	**(N=22)**	**(N=22)**	**(N=21)**	**(N=20)**
Week 1- Week 12 change					
Mean (SE)	-1.54 (0.22)	-1.96 (0.14)	-2.00 (0.14)	-1.96 (0.17)	-1.91 (0.15)
Median	-1.38	-1.82	-2.20	-1.89	-1.86
Week 0-Week 24 change					
Mean (SE)	-4.22 (0.34)	-5.07 (0.34)	-4.79 (0.27)	-5.00 (0.30)	-5.36 (0.33)
Median	-4.16	-4.89	-5.00	-5.31	-5.94
Week 0-Week 52 change					
Mean (SE)	-4.43 (0.45)	-5.72 (0.37)	-5.39 (0.32)	-5.64 (0.34)	-5.91 (0.37)
Median	-4.14	-5.64	-5.88	-5.76	-5.47

At week 52, a notable mean change from baseline in HBV DNA ranging from –5.49 to –6.53 log10 copies/ml was observed in the telbivudine containing groups compared to –4.57 log10 copies/ml in the lamivudine group. The conclusion was similar when the analysis was stratified by baseline ALT level. Results were not significantly different between the pooled comparison of telbivudine 400 and 600 mg dose groups suggesting that the efficacy of the 600 mg telbivudine dose over the 400 mg telbivudine dose is not significantly greater.

In addition, when considering the individual results for HBV DNA reduction, proportionally greater clearance was shown for all four telbivudine arms, compared to the lamivudine monotherapy group in each other AUCMB analysis (Week 0-Week 24 change and Week 0-Week 52 change).

There was no improvement in viral load reduction (as measured by AUCMB methods) with the addition of lamivudine to telbivudine (400 mg/day or 600 mg/day) compared to the results for telbivudine alone.

Overall 21% of patients experienced at least one drug-related AE and the overall incidence of drug-related AE did not differ significantly across the five treatment groups.

Considering that the results could not exclude the modest (0.2 log10, ~40%) efficacy advantage for the 600 mg/day dose predicted by the Emax modeling of the Phase I/II trial data and that there were no apparent dose-related clinical AEs or laboratory abnormalities in the Phase IIb trial, the applicant selected the 600 mg/day telbivudine dose to conduct the pivotal phase III trial versus lamivudine monotherapy (100 mg/day). The choice of 600 mg for the Phase III study which may be regarded as a conservative attitude, appeared acceptable.

Study NV-02B-010 two-year extension of study NV-02B-003

Out of 104 patients enrolled in the [NV-02B-003] trial (ITT populations) 90 subsequently enrolled in the [NV-02B-010] two-year extension study, which corresponded to the PP populations. The pre-specified interim analysis after 104 weeks of treatment (from Baseline in [NV-02B-003]) was provided. The primary endpoint for this first interim analysis is the reduction of HBV DNA levels from Baseline to nominal Week 104.

At week 104, the notable mean change from baseline in HBV DNA that was observed at week 52 was still maintained ranging from –5.3 to –5.5 log10 copies/ml in the telbivudine 600 mg containing groups (ITT population) compared to –3.8 log10 copies/ml in the lamivudine group. In the PP populations, the same trend was observed.

By nominal Week 104, HBeAg seroconversion occurred in 38.1% of telbivudine recipients, 24.4% of patients on combination therapy, and 22.2% of lamivudine recipients. The proportion of

seroconverters increased over the second year of therapy in both telbivudine (31.0% to 38.1%) and combination (14.6% to 24.4%) groups from nominal Weeks 52 to 104. HBeAg seroconversion rates for patients receiving lamivudine therapy group did not increase over this time period.

At Week 96, fewer patients on telbivudine (20%) experience virologic breakthrough compared to patients on lamivudine (32%) and combination therapy (33%). Results are nonetheless difficult to interpret because of the limited number of patients.

A statement has therefore been introduced in the SPC highlighting that the therapeutic response observed with the combination telbivudine and lamivudine was lower than that with telbivudine monotherapy and therefore telbivudine is not recommended to be used with lamivudine.

Main study NV-02B-007

METHODS

This is an ongoing 104-week, phase III, randomised, double-blind, multicentre, international clinical trial designed to compare the efficacy and safety of telbivudine to lamivudine.

Study Participants
The population targeted in this study was a mixed population of HBeAg-positive and -negative HBV infected patients.
Eligible patients were aged 16-70 years and at the screening visit (up to 7 weeks pre-randomisation) had:

- Documented chronic hepatitis B (CHB), defined by:
  - clinical history compatible with CHB
  - detectable serum HBsAg
  - HBeAg-positive or HBeAg-negative
  - ALT 1.3-10 x ULN
  - liver biopsy within 12 months prior to randomisation with histology compatible with CHB (five unstained formalin fixed slides were to be available at the investigator's site prior to randomisation).
- Compensated liver disease
- No prior nucleoside/nucleotide analogue therapy at any time and no interferon alfa or other immunomodulators for at least one year before screening for this study.
- HBV DNA ≥ 6 log10 copies/ml (by central laboratory COBAS Amplicor HBV Monitor assay)

The most notable exclusion criteria were:
- Co-infection with HCV, HDV, HIV-1 or HIV-2
- Any history/evidence of hepatic decompensation or hepatocellular carcinoma (HCC)
- Known primary or secondary causes of liver disease other than hepatitis B (except Gilbert's syndrome and Dubin-Johnson syndrome did not exclude patients)
- History of clinical pancreatitis

Treatments
Patients were randomised to receive telbivudine 600 mg (Group A) + or lamivudine 100 mg once daily (Group B). Treatments were to be taken in the morning without regard to food intake.

Treatment discontinuation (without study discontinuation) was available (but not mandated) at week 52 or later if the patients met the criteria for virologic response:

- For HBeAg-positive patients at entry, the patient had exhibited loss of HBeAg for at least 24 weeks and the patient's HBV DNA level was <5 log10 copies/ml.
- For HBeAg-negative patients at entry, the patients had to achieve confirmed HBsAg loss at or after Week 52 on two consecutive visits.

These patients were to continue with normal study assessments and restart the same blinded therapy if they experienced a post-treatment disease relapse.

Objectives

The primary objectives were:

- To investigate the clinical efficacy of telbivudine and lamivudine in adults with compensated HBeAg-positive and HBeAg-negative CHB over two years (104 weeks).
- To compare safety between the two treatments.

The secondary objectives were:

- To assess the post-treatment durability of the virological response (loss of detectable serum HBeAg with serum HBV DNA <5 log10 copies/ml) in the subgroup with HBeAg-positive CHB.
- To compare the frequency of virological breakthrough during two years of treatment and its clinical correlates.
- To characterise treatment-emergent HBV associated with virological breakthrough.

Outcomes/endpoints

The primary efficacy variable was the therapeutic response defined as serum HBV DNA < 5 log10 copies/ml associated with either HBeAg loss or ALT normalisation at week 52.

Other efficacy variables

The main secondary endpoint was histological response was defined as at least 2-point reduction in the Knodell necroinflammatory score with no worsening in the fibrosis score.

Other secondary efficacy variables included:

- Magnitude of HBV DNA reduction
- HBV DNA suppression to <5 log10 copies/ml in patients with ≥6 log10 copies/ml at baseline
- PCTR HBV DNA non-detectable (below LLOQ of 300 copies/ml)
- ALT normalisation
- HBe seroconversion (HBeAg positive only)
- Virologic response (HBeAg positive only) defined as HBV DNA <5 log10 copies/ml and HBe Ag loss
- 3-component HBeAg seroconversion (HBeAg positive only) defined as HBeAg seroconversion and HBV DNA <5 log10 copies/ml
- HBsAg Loss and HBsAg Seroconversion
- Treatment discontinuation due to efficacy (see above)
- Treatment failure
    - Primary = after 24 weeks of treatment, HBV DNA never fell to <5 log10 copies/ml for two consecutive visits after the start of study treatment
    - Secondary = Week ≥24 ALT increases to 10 × ULN or is ≥2 × ULN for 16 weeks and HBV DNA is ≥6 log10 copies/ml or meets the definition of virological breakthrough
        - OR discontinuation for disease progression
        - OR discontinuation for lack of efficacy after Week 24
        - OR discontinuation at a time when ALT ≥2 × ULN and HBV DNA is ≥6 log10 copies/ml or meets the definition of virological breakthrough
    - Virological breakthrough
        - For those who attained HBV DNA suppression, this was defined as HBV DNA ≥5 log10 copies/ml on two consecutive visits with no more than one subsequent value <5 log10 copies/ml or HBV DNA ≥5 log10 copies/ml at the last treatment visit.
        - For those who did not attain HBV DNA suppression but achieved ≥2 log10 copies/ml reduction this was defined as a return of HBV DNA to within 1 log10 copies/ml of baseline on two consecutive visits with no more than one subsequent level >1 log10 copies/ml below baseline or a single HBV DNA level within 1 log10 copies/ml of baseline at the last treatment visit

- Treatment-emergent HBV resistance defined as virological breakthrough by Week 48 with genotypic evidence of resistance-associated mutations in HBV DNA amplified from patient sera.

Liver biopsy samples were to be obtained pre-treatment and at Week 52 during treatment. Histology slides were scored for necroinflammatory and fibrotic activity using the Knodell and Ishak scoring systems.

Sample size
The sample size calculations were based on accruing at least 1200 patients, with at least 600 HBeAg-positive patients and at least 400 HBeAg-negative patients. For the therapeutic response endpoint, this sample size provided 99% power for the non-inferiority claim, with an assumption of a 15% non-inferiority criterion, and 92% power for the superiority claim if the response rate on telbivudine is 15% better than lamivudine. The study was adequately powered overall as well as for the sub-populations of HBeAg positive and HBe-Ag negative separately at one year for the primary and the key secondary endpoints.

Randomisation
Randomisation was performed via an IVRS system to assign patients (1:1) to the two treatments.
There was also stratification according to:

- HBeAg positive or negative
- ALT <2.5 x ULN or ALT ≥2.5 x ULN

Blinding (masking)
This study was to be performed in a double-blind manner. There was an external Data Safety Monitoring Board (DSMB).

Statistical methods
The primary analysis population for all non-inferiority and superiority tests of efficacy endpoints was the Intent-to-treat (ITT) ITT population. The secondary analysis population for all non-inferiority tests of efficacy endpoints was the Efficacy-evaluable (EE) population.

The Histological Response populations comprise all patients in the ITT population who had evaluable pre-treatment liver biopsies = the modified ITT (mITT) population for assessment of Histological Response. Patients from the EE population whose baseline liver biopsy had a Knodell HAI score >3 = the modified EE (mEE) population for assessment of Histological Response.

With the exception of the criteria for treatment discontinuation, breakthrough, HBV resistance and treatment failure, missing categorical data were to be excluded from the EE analyses (i.e., missing = missing) and treated as no response (i.e., missing = failure) in the ITT analyses. For the efficacy parameters of virologic breakthrough, HBV resistance and treatment failure, the LOCF method was used for missing data in both the ITT and EE analysis. For missing continuous variables, the LOCF method was to be applied in the EE analysis and excluded in the ITT analysis.

The primary analysis was to be conducted after all patients reached Week 52. There were no interim analyses planned or performed. A week 104 analysis will be used to assess longer-term efficacy.
The primary efficacy variable (Therapeutic Response) and the key secondary efficacy variable (Histological Response) were to be analysed according to a 3-step statistical procedure:
1) Separate statistical analysis performed initially for both HBeAg-positive and HBeAg-negative subpopulations

2) If statistical significance was not established within both the HBeAg-positive and HBeAg negative sub-populations, statistical test treatment group interaction between the two HBeAg subpopulations was performed

.
3) If there was no significant treatment interaction between the two subpopulations, a pooled statistical analysis for the overall population was performed. The procedure was to be used initially to test for non-inferiority. If this was successful it was to be repeated to test for superiority. A positive test for

non-inferiority required the confidence interval to be entirely above -15%. A positive test for superiority required the confidence interval to exclude 0%. The testing procedure outlined allows for an overall conclusion of non-inferiority or superiority but not for separate conclusions for each sub-population. The non-inferiority margin of 15% was selected by referring back to past placebo controlled trials of lamivudine against placebo.

RESULTS

At the time of the submission of the application, 52 weeks results were provided for the overall population as the basis for the efficacy assessment. Preliminary results at weeks 76 for a very limited proportion of the population enrolled were also submitted.

Supplementary data on the long term efficacy and safety (complete 76 weeks results as well as preliminary Week 104 results) were submitted, during the procedure.

Participant flow

Out of the 1367 patients included in the study, the ratio was approximately 70/30 % in favour of HBeAg positive (921 randomised as HBeAg positive versus 446 as HBeAg negative).

The disposition of patients is presented in table 5. Overall a large proportion of patients completed 52 weeks period.

Of the 37 ITT patients not included in the EE population (18 telbivudine and 19 lamivudine) the reasons were retrospective failure to meet the criteria for documented CHB, prior prohibited treatment for CHB, other causes of liver disease or non-compliance.

Table 5: Patient disposition up to week 52

	Lamivudine		Telbivudine		Total	
Patient populations	N	(%)	N	(%)	N	(%)
ITT & Safety populations	687	(100)	680	(100)	1367	(100)
EE population	668	(97)	662	(97)	1330	(97)
Reason for study discontinuation	**n**	**%**	**n**	**%**	**n**	**%**
ITT & Safety populations – any reason	32	(4.7)	18	(2.6)	50	(3.7)
Non-compliance	3	(0.4)	3	(0.4)	6	(0.4)
Pregnancy	2	(0.3)	1	(0.1)	3	(0.2)
Adverse event(s)	5	(0.7)	2	(0.3)	7	(0.5)
Clinical disease progression	2	(0.3)	0		2	(0.1)
Lack of efficacy after Week 24	1	(0.1)	0		1	(0.1)
Death	1	(0.1)	0		1	(0.1)
Request	18	(2.6)	12	(1.8)	30	(2.2)
EE population - any reason	30	(4.5)	16	(2.4)	46	(3.5)
Non-compliance	2	(0.3)	3	(0.5)	5	(0.4)
Pregnancy	2	(0.3)	1	(0.2)	3	(0.2)
Adverse event(s)	5	(0.7)	2	(0.3)	7	(0.5)
Clinical disease progression	2	(0.3)	0		2	(0.2)
Lack of efficacy after Week 24	1	(0.1)	0		1	(0.1)
Death	1	(0.1)	0		1	(0.1)
Request	17	(2.5)	10	(1.5)	27	(2.0)

Baseline data

Patients were well balanced between treatment groups for baseline characteristics (table 6).

Table 6: ITT population demographics

Parameter	Lamivudine N=687	Telbivudine N=680	Total N=1367
Age (years)			
mean (SE)	36.2 (0.46)	35.5 (0.45)	35.8 (0.32)
median	35.0	34.0	34.0
25%, 75%	26.0, 45.0	26.0, 44.0	26.0, 44.0
range	16.0, 68.0	16.0, 68.0	16.0, 68.0
Gender, n (%)			
Male	529 (77.0)	507 (74.6)	1036 (75.8)
Female	158 (23.0)	173 (25.4)	331 (24.2)
Race, n (%)			
Caucasian	111 (16.2)	98 (14.4)	209 (15.3)
Asian*	515 (75.0)	525 (77.2)	1040 (76.1)
African/African/American	10 (1.5)	7 (1.0)	17 (1.2)
Hispanic/Latino	8 (1.2)	4 (0.6)	12 (0.9)
Middle East./Indian Subcontinent Other	11 (1.6)	14 (2.1)	25 (1.8)
races	32 (4.7)	32 (4.7)	64 (4.7)

*Chinese, Korean, Thai, Japanese, Vietnamese, Filipino, Malay, and other Asian

The vast majority of the population enrolled was Asian. Overall, 98 Caucasians patients included in the study have received telbivudine.

With respect to HBV baseline characteristics, as expected in a majority of patients of Asian ethnicity, the majority of patients are infected with HBV genotypes B (26%) or C (51%).

Within each of the HBeAg positive and negative groups the features of the HBV-related histories showed only minor differences between treatments. Most patients had an "unknown" route of HBV transmission.

HBeAg-positive population have much higher pre-treatment HBV DNA levels than the HBeAg-negative population.

Most patients enrolled had ALT > 2 x ULN but almost all has normal albumin and bilirubin at baseline. ALT data at baseline showed no notable differences between treatment of between HBeAg positive or negative.

An overview of the baseline serologic markers and liver function parameters is presented in table 7.

Table 7

	Baseline HBV serologic markers and liver function parameters - HBeAg-negative ITT population				Baseline HBV serologic markers and liver function parameters - HBeAg-positive ITT population			
Laboratory parameter	**Lamivudine (N=224)**	**Telbivudine (N=222)**	**Total (N=446)**	**p-value***	**Lamivudine (N=463)**	**Telbivudine (N=458)**	**Total (N=921)**	**p-value***
HBsAg, n (%)								0.3197
positive	224 (100)	222 (100)	446 (100)		462 (100)	458 (100)	920 (100)	
negative	0	0	0		1 (0)	0	1 (0)	
HBsAb, n (%)				0.8065				0.5297
positive	8 (4)	7 (3)	15 (3)		21 (5)	17 (4)	38 (4)	
negative	216 (96)	215 (97)	431 (97)		442 (95)	441 (96)	883 (96)	
HBeAg, n (%)				0.2355				0.4313
positive	4 (2)	8 (4)	12 (3)		442 (95)	432 (94)	874 (95)	
negative	220 (98)	214 (96)	434 (97)		21 (5)	26 (6)	47 (5)	
HBeAb, n (%)				0.3519				0.8981
positive	220 (98)	215 (97)	435 (98)		63 (14)	61 (13)	124 (13)	
negative	4 (2)	7 (3)	11 (2)		400 (86)	397 (87)	797 (87)	
HBV DNA				0.1189				0.8444
mean (SE), log10 copies/ml	7.42 (0.102)	7.66 (0.118)	7.54 (0.078)		9.53 (0.092)	9.51 (0.085)	9.52 (0.063)	
median	7.12	7.21	7.18		9.57	9.57	9.57	
ALT, IU/l				0.5477				0.1269
mean (SE)	143.7 (8.74)	137.0 (6.94)	140.4 (5.58)		158.9 (6.30)	146.2 (5.36)	152.6 (4.14)	
median	98.5	99.0	99.0		111.0	110.5	111.0	
ALT Categories (IU/l)				0.6157				0.5993
<1 x ULN, n (%)	15 (7)	18 (8)	33 (7)		17 (4)	14 (3)	31 (3)	
1 x ULN to <2 x ULN, n (%)	84 (38)	74 (33)	158 (35)		153 (33)	149 (33)	302 (33)	
2 x ULN to <5 x ULN, n (%)	88 (39)	98 (44)	186 (42)		204 (44)	219 (48)	423 (46)	
5 x ULN, n (%)	37 (17)	32 (14)	69 (15)		89 (19)	76 (17)	165 (18)	
mean (SE) - x ULN	3.14 (0.185)	2.98 (0.144)	3.06 (0.117)	0.5010	3.52 (0.140)	3.27 (0.117)	3.39 (0.092)	0.1694
Albumin, g/dl				0.3365				0.1359
mean (SE)	4.37 (0.024)	4.40 (0.024)	4.39 (0.017)		4.42 (0.018)	4.46 (0.018)	4.44 (0.013)	
median	4.35	4.40	4.40		4.40	4.45	4.40	
Bilirubin, mg/dl				0.7019				0.1751
mean (SE)	0.75 (0.023)	0.74 (0.025)	0.74 (0.017)		0.78 (0.016)	0.75 (0.016)	0.76 (0.011)	
median	0.70	0.70	0.70		0.70	0.70	0.70	
*χ 2 test.								

Based on availability of paired liver biopsies, the mITT population for histological analyses included 753/872 (86.4%) patients in the HBeAg-positive population and 394/430 (91.6%) patients in the HBeAg-negative population (table 8).

Table 8

	HBeAg-positive		**HBeAg-negative**	
	Lamivudine	Telbivudine	Lamivudine	Telbivudine
Histology evaluation	(n=433)	(n=439)	(n=218)	(n=212)
Knodell HAI, total or component, mean				
Total HAI score (sum of I-IV)	9.0	8.9	9.6	9.0
Necroinflammatory score (sum of I-III)	7.3	7.4	7.6	7.3
I. Periportal +/- bridging necrosis	2.8	2.8	2.9	2.8
II. Intralobular degeneration & focal necrosis	1.9	2.1	2.0	1.9
III. Portal inflammation	2.6	2.6	2.7	2.6
IV. Fibrosis	1.6	1.5	1.9	1.7
Ishak fibrosis score	2.2	2.1	2.5	2.3

The number of patients with cirrhosis was low: 2.8% (37/1302) of patients enrolled with evaluable baseline biopsy had cirrhosis (Ishak score >5). Of these, 21 patients (3.2%; 21/651) were in the lamivudine treatment arm, and 16 patients (2.5%; 16/651) were in the telbivudine treatment arm. When evaluated by HBeAg status, 2.1% (18/872) of HBeAg positive patients had cirrhosis, while 4.4% (19/430) of HBeAg negative patients had cirrhosis.

The majority of patients did not receive previous interferon therapy. Of the 5.9% of patients (HBeAg-positive) and 11.2% (HBeAg-negative) who were previously treated with interferon, most had failed on an efficacy basis, rather than an intolerance basis

Recruitment
Most patients were enrolled in Asia (62%), North America (12%), the antipodes (11%) and from Europe (15%). However, with 112 sites, the numbers enrolled by site were often very small (single digits). The largest contributors were China (27%), Hong Kong and Taiwan (both 8%).

Conduct of the study
There was no amendment to the protocol. Protocol deviations were infrequent (<7%) across groups and generally similar between treatments except that four in the lamivudine group were censored after commencing adefovir.

An inspection was performed at the EMEA request to assess the GCP standards in investigator sites in Thailand and China. This inspection was aimed at confirming the reliability of data in the submitted application for marketing authorisation. Overall, this inspection confirms that the study was performed in line with the GCP.

Two significant issues were nevertheless detected:

- the tendency of investigators to not notify the extreme value of laboratory abnormalities if they were not judged as clinically significant. However, given that Grade3/4 laboratory abnormalities were recorded and discussed in the CSR (regardless of their clinical significance and their notification as an AE by the investigator) and given that both study arms were supposed to be similarly impacted due to the double blind design of the study, this could not be considered as a major issue in the interpretation of the safety results.

- the lack of supporting documentation for medical histories of patients (medical history were obtained by the patient verbal account). The number of patients who might potentially have not been naïve of antiviral is expected to be marginal since previously treated patients are expected to be well identified by the medical team. Moreover, since telbivudine monotherapy is not expected to be effective in resistant patients, this is not expected to have significantly favoured the telbivudine arm.

Outcomes and estimation
The statistical significance for therapeutic response at week 52 was not established in both HBeAg positive and HBeAg negatives subpopulation so the statistical test for treatment group interaction between both subpopulations was performed. The HBeAg status interaction precluded any investigation of the efficacy results with a pooled analysis as planned in the protocol. The efficacy analyses were consequently displayed for the HBeAg-positive and HBeAg-negative populations respectively as if two distinct studies had been performed. This is acceptable since HBeAg subgroups have now been established as 2 distinct disease entities.

Primary endpoint
Week 52 results on the primary endpoint displayed in table 9 showed whatever the population analysed (ITT or EE), the non-inferiority of telbivudine over lamivudine, both for HBeAg- positive and -negative patients.

When testing for superiority, results showed the superiority of telbivudine treatment only in the HBeAg-positive group.

Table 9: Primary efficacy endpoint (therapeutic response at week 52)

POPULATION	**HBeAg positive**		**HBeAg negative**	
TREATMENT	**LdT 600mg**	**LAM 100 mg**	**LdT 600mg**	**LAM 100 mg**
Therapeutic response at week 52 N(%) ITT population	345/458 (75.3)	310/463 (67.0)	167/222 (75.2)	173/224 (77.2)
Difference (LdT – LAM) 95.68 % CI (p-value)	(2.4,14.2) p=0.0047*		(-10.2,6.1) p=0.6187	
Therapeutic response at week 52 N (%) EE population	334/434 (77.0)	299/445 (67.2)	174/228 (76.3)	180/223 (80.8)
Difference (LdT – LAM) 95.68 % CI** (p-value)	(4.0, 15.9) p= 0.0007		(-12.3, 3.3) p = 0.2461	

*LdT was superior to LAM
**Adjusted for multiple comparisons

Across ITT and EE, analysis results confirmed that therapeutic response was in favour of telbivudine whatever the strata (ALT<2.5 and ALT≥2.5x ULN) although it appeared somewhat better for patients in the high ALT/HBeAg positive and high ALT/HBeAg negative strata.

Key secondary endpoints
When considering the secondary efficacy endpoints (virological, biochemical and histological), consistent results were observed through the analyses that demonstrated either the non-inferiority of telbivudine versus lamivudine (with a trend in favour of telbivudine) or the superiority of telbivudine at week 52.

Histologic response

Telbivudine achieved better histologic response than lamivudine as shown in table 10.

Table 10

POPULATION	**HBeAg positive**		**HBeAg negative**	
TREATMENT	**LdT 600mg**	**LAM 100 mg**	**LdT 600mg**	**LAM 100 mg**
Histologic improvement at week 52 N(%) mITT pop	**284/439 (64.7)**	**244/433 (56.3)**	**141/212 (66.6)**	**144/218 (66.0)**
Difference (LdT – LAM) 95.68 % CI (p-value)	(2.4,14.7) p=0.0105*		(-8.3,9.5) p=0.8994	
Histologic improvement at week 52 N(%) mEE	274/384 (71.5)	237/386 (61.3)	141/199 (70.8)	144/207 (69.7)

Difference (LdT – LAM) 95.68 % CI (p-value)	3.6, 16.8 p =0.0024	-7.7, 10.0 p =0.7984

Telbivudine recipients had proportionally greater reductions in mean total Knodell HAI scores, in both the HBeAg-positive and HBeAg negative patient populations, compared to lamivudine recipients (for HBeAg-positive:-3.92 vs. - 3.64 in mITT analysis, and -4.49 vs. – 4.02 in mEE analysis; for HBeAg-negative: - 3.85 vs. -3.73 in the mITT analysis, and -4.21 vs. -3.89 in mEE analysis).

With regard to changes in fibrosis, the treatment effects appeared similar at one year for telbivudine and lamivudine. Patients with baseline Ishak scores > 3 had median scores declines of – 1.0 at week 52 while those with baseline scores ≤ 3 had no change in median scores with either telbivudine or lamivudine.

Table 11: Summary of changes in Ishak fibrosis scores

Change	Lamivudine	Telbivudine	95% CI	p-value
mITT HBeAg-positive	N=433	N=439		
Improved, n (%)	189 (43.6)	166 (37.8)	-12.5, 0.6	0.0774
No change, n (%)	143 (33)	175 (40)		
Worsened, n (%)	37 (9)	43 (10)		
Missing Week 52 biopsy, n (%)	64 (15)	55 (13)		
mITT HBeAg-negative	N=-218	N=212		
Improved, n (%)	99 (45.4)	100 (47.1)	-7.7, 11.1	0.7209
No change, n (%)	90 (41)	69 (33)		
Worsened, n (%), n (%)	11 (5)	25 (12)		
Missing Week 52 biopsy, n (%)	18 (8)	18 (8)		
mEE HBeAg-positive	N=386	N=384		
Improved, n (%)	181 (46.8)	160 (41.8)	-12.0, 2.0	0.1601
No change, n (%)	122 (32)	148 (39)		
Worsened, n (%)	27 (7)	30 (8)		
Missing Week 52 biopsy, n (%)	56 (15)	46 (12)		
mEE HBeAg-negative	N=207	N=199		
Improved, n (%)	93 (44.9)	97 (48.8)	-5.8, 13.6	0.4290
No change, n (%)	89 (43)	67 (34)		
Worsened, n (%)	11 (5)	18 (9)		
Missing Week 52 biopsy, n (%)	14 (7)	17 (9)		

Virological response

Telbivudine achieved better response than lamivudine in terms of virologic efficacy as shown in table 12.

Table 12

	HBeAg positive			HBeAg negative		
Reduction in HBV DNA (log 10 copies/ml) ITT population	Lamivudine	Telbivudine	p-value	Lamivudine	Telbivudine	P-value
Week 52	N=444	N=443		N=219	N=219	
mean (SE) median	-5.5 (0.12) -5.9	-6.4 (0.09) -6.7	<0.0001	-4.4 (0.14) -4.5	-5.2 (0.13) -5.0	<0.0001

Proportion of patients with PCR-non-detectable HBV DNA by study visit, by HBeAg status - ITT	

population						
Week 52	**N=463**	**N=458**		**N=224**	**N=222**	
n (%)	**187 (40.4)**	**275 (60.0)**	**<0.0001**	**160 (71.4)**	**196 (88.3)**	**<0.0001**

The proportion of patients who achieved specific HBV DNA levels at week 52 demonstrated a consistent advantage in the telbivudine group.

HBeg responses

The better virological response is not translated into a higher rate of HBe seroconversion as compared with lamivudine as shown in table 13.

Table 13: HBeAg loss and seroconversion at week 52 - ITT population

	Lamivudine	Telbivudine		
	n/N (%)	n/N (%)	95% CI	p-value*
HBeAg loss				
Week 52	103/442 (23.3)	111/432 (25.7)	-3.2, 8.1	0.4038
HBeAg seroconversion				
Week 52	95/442 (21.5)	97/432 (22.5)	-4.3, 6.4	0.7263

*Treatment group differences controlled for randomization strata: difference between proportions

When HBeAg loss by Week 52 is analysed by the degree of viral load reduction achieved, there is a clear association between greater suppression of viral load and likelihood of HBeAg loss. Almost half of the patients who achieved a viral load of <300 copies/ml (undetectable per the assay used) achieved HBeAg loss compared to 3% of those with > 4 log10 copies/ml at Week 52.

Change in serum ALT

There was no statistical difference across treatment in the proportion of patients with ALT normalisation (table 14).

Table 14: ALT normalisation – ITT population

	Lamivudine n/N (%)	**Telbivudine** n/N (%)	**95% CI**	**p-value***
HBeAg-positive				
Week 52	334/446 (74.9)	340/440 (77.2)**	-3.3, 7.9	0.4172
HBeAg-negative				
Week 52	161/203 (79.3)**	151/203 (74.4)	-13.0, 3.2	0.2385

*Treatment group differences controlled for randomisation strata.
**Patients with ALT <1 x ULN at Baseline excluded from analysis

Long term efficacy

Analysis of maintained on-treatment response up to week 104 was performed for the primary efficacy endpoint, therapeutic response, and for key secondary efficacy endpoints of HBV DNA undetectable, ALT normalisation and HBeAg loss. Preliminary results showed that telbivudine treated patients exhibited higher degree of maintained responses on all the key efficacy measures examined (table 15)**.** This was confirmed in both HBeAg positive and negative patient populations.

Table 15: Summary of Maintained Efficacy Outcome at Week 104* - ITT Patients

Maintained Efficacy Response	HBeAg Positive		HBeAg Negative	
	LdT (N=458)	Lam (N=463)	LdT (N=222)	Lam (N=224)
Therapeutic Response	58.7%	45.4%	70.7%	56.7%
HBV DNA Undetectable	50.2%	36.1%	77.5%	50.0%
ALT Normalisation	63.9%	56.5%	70.9%	58.0%

HBeAg loss	32.6%	27.4%	NA	NA

* Week 104 preliminary data with data cut off August 23rd, 2006.

There are currently no sufficient data to allow assessment of the durability of off-treatment efficacy responses of telbivudine.

Ethnicity

The influence of ethnicity on telbivudine pharmacokinetics was assessed in the population pharmacokinetic analysis already described in section II.1. Of the 363 subjects that provided data for the final model, 126 (34.7%) were Caucasian, 41 (11.3%) were of African descent, 105 (28.9%) were Hispanic/Latino, 66 (18.2%) were Chinese, 24 (6.61%) were Japanese and 1 (0.28%) was American Indian. The estimates of oral clearances (mean ± SD; l/hr) were 17.8 for Caucasians, 18.8 for those of African descendent, 20.9 for the Hispanic/Latinos, 17.8 for the Chinese, 17.4 for the Japanese and 19.4 for the American Indians. The applicant concluded that the pharmacokinetic variability of telbivudine was small and that the pharmacokinetic differences due to the ethnic and racial effects were relatively minor and not clinically relevant. The clinical pharmacology of telbivudine has been demonstrated to be ethnically insensitive, with comparable levels of systemic exposure at comparable dosing levels, in Asian and Caucasian patients. In line with the ICH E5 guideline pertaining to foreign data, the applicant concluded that telbivudine meets the ICH criteria for lack of ethnic sensitivity.

Although quite large, the study NV-02B-007 was not statistically powered to assess treatment effects with patient subgroups such as ethnic subgroups.

There was a concern that the clinical data derived from European/Caucasian patients were currently too limited (n=98 patients treated with telbivudine) to properly assess the benefit/risk in this population. There was also a concern that, especially for HBeAg negative patients, the risk/benefit relationship might favour use of lamivudine over telbivudine. Within the HBeAg positive Caucasian patients, therapeutic response in the lamivudine group (55.5%) was quite similar to the telbivudine group (59.5%) (difference 4% ; p=0.6735).

However, in the HBeAg negative population, results for therapeutic response were close to statistical significance in favour of lamivudine (78.7%) compared with telbivudine (63.0%) (difference –15.8% ; p=0.0804)

To provide further reassurance with regard to efficacy in HBeAg negative Caucasians preliminary 104 weeks results were submitted (table 16).

The trend towards a lower therapeutic response observed in the 52 weeks report in the subgroup of HBeAg negative Caucasian patients was no longer apparent with the 104 weeks results. In line with the results on the overall population, the apparent superiority of telbivudine over lamivudine has also become true in this subgroup. As explained by the applicant, such a change was mainly driven by the results on ALT normalisation. Indeed, within the 52 weeks results, an unexpectedly high rate of ALT normalisation was observed in the lamivudine arm, leading to a superior (composite) therapeutic response in this arm, despite the better virologic response in the telbivudine arm.

At week 104, the reverse was observed as regards the ALT normalisation, and as a consequence the superiority of telbivudine over lamivudine was achieved.

Table 16: Caucasian HBeAg Negative Patients Week 52 and Week 104 – ITT Population

Endpoint	Telbivudine		Lamivudine	
	Week 52 (n=46)	Week 104* (n=46)	Week 52 (n=56)	Week 104* (n=56)
TR (%)	63	69	79	61
HBV DNA reduction from Baseline (log10)	-5.43	-5.05	-4.21**	-3.55**

PCR neg (%)	82	69	65**	46**
ALT norm (%)	61	71	81	66
Source: T2.01.19_EFF_RACE				

* Preliminary data ** p <0.05

Finally it was observed that the therapeutic response for both telbivudine and lamivudine was lower in Caucasian patients than in Asian patients.

HBV genotype

Genotypes B and mainly C are preponderant in Asian patients while genotype A, which is the more frequent in Europe, is included within the "other" HBV genotype category.

Table 17: Proportion of patients with results by genotype– ITT Population Week 52

Outcome	HBeAg-positive		HBeAg-negative	
	Lamivudine	Telbivudine	Lamivudine	Telbivudine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Therapeutic Response				
Genotype B	81/113 (71.4)	99/129 (77.1)	48/59 (81.4)	47/59 (79.8)
Genotype C	180/258 (70.0)	205/259 (79.0)	67/86 (78.1)	72/89 (80.8)
Other	49/92 (52.6)	41/70 (58.8)	58/79 (73.4)	48/73 (65.7)
Histological Response				
Genotype B	56/105 (53.1)	72/124 (58.2)	35/59 (59.3)	36/56 (64.3)
Genotype C	143/243 (59.1)	177/248 (71.2)	63/84 (75.0)	61/84 (72.6)
Other	45/85 (52.4)	35/67 (52.8)	46/75 (61.4)	44/71 (62.4)
Undetectable HBV DNA				
Genotype B	46/113 (40.5)	72/129 (56.3)	47/59 (79.7)	53/59 (89.9)
Genotype C	109/258 (42.5)	170/259 (65.4)	63/86 (73.5)	84/89 (94.3)
Other	32/92 (34.5)	33/70 (47.6)	50/79 (62.9)	59/73 (80.8)
ALT normalisation				
Genotype B	88/109 (80.7)	100/124 (81.3)	41/50 (82.0)	39/50 (78.0)
Genotype C	194/248 (78.5)	198/249 (79.5)	65/82 (79.5)	69/86 (80.1)
Other	52/89 (58.1)	42/67 (62.8)	58/75 (77.3)	43/66 (65.2)

HBV genotype comparisons showed that rates for therapeutic and histological responses and ALT normalisation were similar or at least numerically better with telbivudine within all three HBV genotype groups (B, C and other) in the HBeAg positive population but there were inconsistent patterns seen between treatments in the HBeAg negative group. Percentages achieving undetectable HBV DNA were consistently higher with telbivudine regardless of HBeAg status.

The CHMP considered that the limited number of European/Caucasian patients was a concern as regard to the under-representativity of "European" genotypes such as A.

Other analyses

At the request of the CHMP, the applicant submitted the results using for the primary efficacy variable a "Combined Response" endpoint comprising ALT normalisation (for those patients with elevated pretreatment ALT), loss of HBeAg in HBeAg-positive patients or a decrease in HBV DNA to <5 log10 copies/ml, and histologic improvement (defined as a two point or greater improvement in Knodell necroinflammatory score with no worsening in fibrosis) as now recommended in the CHMP "Guideline for the Clinical Evaluation of Medicinal Products Intended for Treatment of Hepatitis B,". (2006).
The re-analysis showed that telbivudine retained superiority over lamivudine in HBeAg-positive patients and non-inferiority in HBeAg-negative patients as shown in the table 18.

Table 18: Combined Response Rates in MITT and MEE populations by HBe antigen status and Treatment

	HBeAg-positive			HBeAg-negative		
Population	LAM	LdT	P values	LAM	LdT	P value
mITT	187/433 (43.2%)	233/439 (53.1%)	0.0028	122/218 (55.9%)	112/212 (52.9%)	0.5324
mEE	180/386 (46.4%)	227/384 (59.2%)	0.0003	124/207 (60.0%)	112/199 (56.3%)	0.4388

*Combined response rate is defined as ALT normalization and Histologic Response with either HBeAg loss or suppression of HBV DNA <5 log10 copies/ml

**missing data treated as failure

Further analyses were undertaken using the EMEA defined Combined Response but adjusting the HBV DNA threshold to <4, <3 $\log_{10}$ copies/ml and <300 copies/ml (undetectable), respectively. In HBeAg-positive patients, the difference in response rates between the two treatment arms widened as the threshold for HBV DNA reduction was lowered while always remaining statistically significant, demonstrating the superiority of telbivudine over lamivudine. In HBeAg-negative patients, the difference between the two treatment arms was gradually obliterated as the HBV DNA criterion became more restrictive and the p value nears 1, showing that the two treatments are equally effective. The results of the logistic multivariate analysis confirmed the predictive relationships of baseline serum ALT and HBV DNA level and therapeutic response at week 52 in both HBeAg positive and HBeAg negative patients.

For both HBeAg-positive and HBeAg-negative patients, greater reductions in HBV DNA (i.e. lower HBV DNA levels) at both Week 12 and Week 24 were highly predictive of increased likelihood of achieving Therapeutic Response at Week 52. HBeAg-positive patients who had achieved undetectable HBV DNA by Week 24 were approximately 18 times more likely to achieve Therapeutic Response than patients whose HBV DNA had not declined below 4 log10 copies/ml. Analysis using weeks 104 outcome demonstrated that week 24 remained a suitable time point for assessing whether treatment was suboptimal using criterion HBV DNA $\geq$ 4 logs at week 24. This has been included in the SPC although the relevance of such criterion in making decision in treatment discontinuation needs to be further evaluated post-authorisation.

Predictor of HBeAg seroconversion

Univariate analysis was performed in order to examine the predictive effect of HBV DNA level at baseline on HBeAg seroconversion. This analysis showed that patients treated with telbivudine who had a baseline HBV DNA level $<10^8$ copies/ml had a significantly higher rate of HBeAg seroconversion at week 52 compared to those patients who at baseline had an HBV DNA level $\geq 10^{10}$ copies/ml: 37.5% vs. 14.1%, respectively. Additionally, a multivariate logistic regression analysis was conducted to further examine the predictive effect of baseline HBV DNA on HBeAg seroconversion in the telbivudine treatment group. The logistic regression model included, in addition to baseline HBV DNA, the following covariates: age, race, gender, weight, BMI, genotype, baseline serum ALT and baseline HAI score in a stepwise selection procedure with p=0.10 to enter and stay. Results showed baseline HBV DNA level and serum ALT to be the only significant ($p<0.01$) predictors of HBeAg seroconversion, and HBV DNA < 8 logs copies/ml to be the strongest predictor of response (odds ratio= 4.65 vs HBV DNA >= 10 logs copies/ml). The analysis was repeated with a further refinement of cut off. Lower baseline HBV DNA level (<9 $\log_{10}$ copies/ml) was again shown to be a strong predictor of HBeAg seroconversion at week 52 and 104. The odds ratios for baseline HBV DNA level < 9 $\log_{10}$ copies/ml vs. $\geq$ 9 $\log_{10}$ copies/ml are 2.24 (p=0.0022) and 2.16 (p=0.0022) for week 52 and 104 respectively.

For baseline ALT level <2 and 2-5 times ULN vs. >5 times ULN, odds ratio was 0.222 and 0.494 respectively.

Other populations

There are currently no available data on the efficacy of telbivudine in HIV co-infected patients, HCV or HDV co-infected patients, liver transplant recipients or children

Clinical safety

Available safety data were collected from the Phase I/II a dose finding trial (NV-02B-001), the international Phase IIb trial (NV-02B-003), and the follow-on (NV-02B-010), the global Phase III (NV-02B-007 also called Globe.

During the procedure, updates were submitted to provide additional safety data on telbivudine at the recommended dose of 600mg.

- Patient exposure

Safety analyses were initially based on data from 1491 patients treated with at least one dose of telbivudine. Approximately 760 patients were treated at the recommended therapeutic dose of telbivudine (600mg/day). Overall, 743 patients were exposed to telbivudine 600mg once daily more than 52 weeks, 268 patients were exposed more than 76 weeks and 64 patients were exposed more than 104 weeks.

Considering that 92% of the patients derived from the main study NV-02B-007 study and only 5% from the smaller Phase IIb study NV-02B-003 and extension phase NV-02B-010, the applicant presented separately the data from these studies in order not to loose data from smaller studies.

Safety updates included complete data up to week 76 (n=1243 patients) and additional partial data up to Week 104 (n=341 patients) for study NV-02B-007 as well as limited longer-term exposure data up to Week 156 for study NV-02B-003/NV-02B-010 (n=58).

The applicant has also presented pooled data for week 52 data from the phase III Chinese study NV-02B-015 in 336 patients. These did not raise any new concern and are not discussed here. Overall, up to the data cut-off of this safety update (i.e 1st November 2005), 898 patients were exposed to telbivudine 600mg once daily more than 52 weeks, 686 patients were exposed more than 76 weeks, 218 patients were exposed more than 104 weeks and 26 patients were exposed more than 156 weeks.

Overall, the safety population included mostly Asian male patients. HBe Ag positive represent 65.4 % of patients in the telbivudine group and 66 % of patients in the lamivudine group. Caucasian patients represent only 15% of the main study population.

- Adverse events

Incidences of adverse events (AEs), treatment-related AE, severe Grade 3-4 AE, death and serious adverse events (SAE) reported in the study NV-02B-007 from baseline to week 52, baseline to week 76 and from week 52 to week 104 as well as the data reported during study NV-02B-003 (from baseline to week 52) and after week 52 in study NV-02B-010 (extension of the NV-02B-003 study) are presented in the tables below.

Table 19: Display of adverse events during NV-02B-007

	LAM N=687	LdT N=680
Baseline to week 52		
Any adverse event	473 (68.9%)	496 (72.9%)
Drug-related AE	132 (19.2%)	161 (23.7%)
Severe Grade 3-4 AE	41 (6%)	31 (4.6%)
Death	1 (0.001%)	0
SAE	33 (4.8%)	18 (2.6%)
Baseline to week 76*		
Any adverse event	513 (74.7%)	536 (78.8%)
Drug-related AE	152 (22.1%)	183 (26.9%)
Severe Grade 3-4 AE	53 (7.7%)	44 (6.5%)
Death	1 (0.001%)	0
SAE	42 (6.1%)	26 (3.8%)
From week 52 to week 104*		
Any adverse event	273 (39.7%)	280 (41.2%)
Drug-related AE	61 (8.9%)	64 (9.4%)
Severe Grade 3-4 AE	18 (2.6%)	20 (2.9%)
Death	1 (0.001%)	0
SAE	9 (1.3%)	8 (1.1%)

*From 120 day safety update

Table 20: Display of adverse events during NV-02B-003 /NV-02B-010 studies

	LAM N=19	LdT 600mg N=44	Combination N=41
Baseline to week 52 (study NV-02B-003)			
Any adverse event	14 (74%)	16/22 (72.7%)	29 (71%)
Drug-related AE	4 (21.1%)	6/22 (27.3%)	7 (17%)
Severe Grade 3-4 AE	1 (5.3%)	2/22 (9.1%)	3 (7%)
Death	0	0	0
SAE	0	1/22 (5%)	1 (2.5%)
From baseline to week 104 (study NV-02B-010)			
Any adverse event	16 (84%)	35/44 (80%)	33 (80%)
Drug-related AE	7 (37%)	12/44 (27%)	7 (17%)
Severe Grade 3-4 AE	4 (21%)	43/44 (6.8%)	3 (7.3%)
Death	0	0	0
SAE	1 (5%)	3/44 (7%)	1 (2%)
Nominal week 104 to nominal week 156 (study NV-02B-010)*			
Any adverse event	3 (15.8%)	16/44 (36.4%)	18 (43.9%)
Drug-related AE	1 (5.3%)	3/44 (6.8%)	4 (9.8%)
Severe Grade 3-4 AE	1 (5.3%)	3/44 (6.8%)	1 (2.4%)
Death	0	0	0
SAE	0	2/44 (4.5%)	0

*From 120 day safety update

The incidence of any adverse events and serious adverse events was comparable between telbivudine group and lamivudine group.

Only one death was reported in both studies and the number of patients with serious or severe adverse events in telbivudine arm remained low here was a slightly higher incidence of treatment-related adverse events in the telbivudine arm compared to the lamivudine arm. These data were confirmed by the complete week 76 data where a trend toward a higher rate of treatment-related adverse events in

telbivudine arm was also observed. In the lamivudine + telbivudine combination arm of study NV-02B-003, the incidence and the severity of adverse events were not increased compared to the administration of both compounds separately.

From week 52 to week 104 (second year of treatment):
In pivotal study, the incidence of any adverse event reported was again comparable between both treatment groups. There was a smaller rate of adverse events reported overall during the second year of treatment (around 40%) than the first year (around 70%) due to the decreasing number of patients with available data over the second year preventing from drawing reliable comparison of the safety profile between the one-year period and the second-year period of the study, as the denominator was not adjusted over time.

When comparing with data derived from the first year of treatment, a higher proportion of patients with serious adverse event was reported in telbivudine-treated patients compared to lamivudine–treated patients although the absolute number remained low in both treatment groups.

These data are in line with those reported during study NV-02B-003 (from baseline to week 52) and after week 52 in study NV-02B-010 (extension of the NV-02B-003 study). Fewer patients reported AEs in the third year of treatment than in previous years since fewer patients contributed to data during the period.

From baseline to week 52, AEs most commonly reported in the telbivudine treated patients were in the following system class categories infections and infestations (35%), gastrointestinal disorders (28 %) and general disorders and administration site conditions (19%). These findings are confirmed by final week 76 data.

In the telbivudine 600mg arm of study NV-02B-003, results by system organ class were overall similar to those observed in main study: adverse events in the SOC gastrointestinal disorders, infections and infestations and nervous systems disorders were the more commonly reported with percentages of 32%, 27% and 27% respectively.

Interim long term data:

- **From Week 52 to Week 104**

Study NV-02B-007:
Again, the most frequently reported adverse events were upper respiratory tract infection (6.0% in the telbivudine arm and 4.5% in the lamivudine arm) and blood creatine phosphokinase (CK) increased (3.8% in telbivudine arm and 3.1% in lamivudine arm). All adverse events were well-balanced between both treatment groups and were in line with the distribution of adverse events reported during the first year of study. However, as already mentioned these data do not concern the totality of included patients and should therefore be taken with caution.

Study NV-02B-010:
The nature of AEs that were observed in the second year of Phase II treatment was similar to that observed in the first year of treatment. One patient in the telbivudine group and 2 patients in the combination group experienced blood CK increased compared to none in lamivudine group.

- **After week 104**

From limited data derived from nominal week 104 to nominal week 156 of study NV-02B-010, a higher proportion of patients experienced adverse events in telbivudine treatment arm (36.4%) versus in the LAM treatment arm (15.8%).

- Treatment related adverse events
  - Study NV-02B-007

The most frequent adverse events occurring in greater than 1% of telbivudine-treated patients with investigator attributability of treatment from baseline to Week 52 is displayed in table 21.

Table 21

	Lamivudine (n=687)		**Telbivudine (n=680)**	
Preferred term	N	(%)	N	(%)
Patients reporting an adverse event	132	(19.2)	161	(23.7)
Blood creatine phosphokinase increased	18	**(2.6)**	34	**(5.0)**
Fatigue	18	(2.6)	29	(4.3)
Headache	27	(3.9)	22	(3.2)
Nausea	15	(2.2)	19	(2.8)
Dizziness	5	(0.7)	10	(1.5)
Diarrhea	4	(0.6)	10	(1.5)
Rash	7	(1.0)	9	(1.3)
ALAT increased	6	(0.9)	7	(1.0)
Blood amylase increased	6	(0.9)	7	(1.0)
Blood lipase increased	7	(1.0)	7	(1.0)
ASAT increased	2	(0.3)	4	(0.6)

Up to week 76 safety data confirmed the baseline to week 52 safety (notably, CK increased related to treatment were again twice reported in telbivudine group compared to lamivudine group (6.3% versus 3.6% respectively).

From week 52 to week 104, 9.4% of telbivudine patients and 8.9% of lamivudine treated patients experienced adverse events possibly or reasonably related to treatment by investigator. Treatment-related blood CK increased were reported in 3.1% of patients in telbivudine group (n=21) and in 1.9% of patients in lamivudine group (n=13).

- Study NV-02B-003

The adverse events most frequently attributed to telbivudine 600mg in study NV-02B-003 were fatigue (9.1%), headache (13.6%) and dyspepsia (4.5%)

- Study NV-02B-010

The adverse events most frequently related to telbivudine 600mg in study NV-02B-010 (nominal week 104 to nominal week 156) were ALAT increased (4.5%, n=2), ASAT increased (2.3%, n=1); HBV DNA increased (2.3%, n=1) and exacerbation of hepatitis B (2.3%, n=1)

A preliminary analysis did not show any relation-ship between dose or duration of telbivudine therapy and an increased incidence of adverse events. The data derived from the second year of the pivotal study and data from studies NV-02B-003 and NV-02B-010 confirmed these findings.

In relation to demographic characteristics, adverse events were proportionally higher with older age, among women and in Caucasian patient compared to Asian patients.
Moreover, prior Week 24 ALT Flares are more common in HbeAg-positive patients than in HbeAg-negative patients.

A more detailed analysis showed that the differences observed in terms of incidence of AEs in telbivudine arm between Caucasian and Asian people are mainly related to the following adverse events:

- Fatigue (14.3% in Caucasian, 9.5% in Asian and 12.3 in other ethnicities)
- Blood CK increased (12.2% in Caucasian, 6.7% in Asian an 17.5% in other ethnicities)
- arthralgia (11.2% in Caucasian, 2.7% in Asian and 2% in other ethnicities)
- headache (18.4% in Caucasian versus 8.2% in Asian versus 12.3% in other ethnicities)

- Serious adverse event/deaths/other significant events

In study NV-02B-007 baseline to week 52, serious adverse events were attributed to treatment in only four patients = 1 patient in lamivudine group (grade 2 urticarial rash) and 3 patients in telbivudine group concerning musculoskeletal disorders and have led to study drug discontinuation or interruption (a grade 2 myopathy, a Grade 1 elevated CK and a Grade 3 elevated CK).

In study NV-02B-003, there was one case of possible treatment-related neuropathy with asymptomatic CK elevation in the telbivudine 600mg + lamivudine group leading to treatment discontinuation.

Longer-term data after 52 weeks from both studies did not show an increase of incidence of serious adverse events with telbivudine.

Overall, no relationship of SAE or other significant adverse events to dose, duration of therapy with telbivudine or lamivudine was evident.

There were some differences in frequency of adverse events in function of HBeAg status (SAE being slightly more frequent in the BeAg-negative patients (6% in LAM group and 3.8% in LdT group in HbeAg-negative patients compared to 4.2% in LAM group and 2.0% in LdT group in HBeAg-positive patients)). Caucasians had higher incidence rates of SAEs than Asians. In addition there were proportionally more adverse events in women than men in the main studies.

So far no death has been attributed to telbivudine.

Two events of special interest have been identified in the telbivudine development programme:
- **ALT flares** since these phenomena are a well-recognized complication of all HBV antiviral agents and represent an important safety issue in the management of chronic HBV infection
- **CK elevations** since these abnormal laboratory values were more commonly reported in telbivudine arm than in lamivudine arm.

ALT flares:

Overall, up to Week 52, ALT flares occurred in about 13% of patients during study NV-02B-007 and were globally more frequently reported in lamivudine treated patients than in telbivudine–treated patients (13.1% versus 10.3%).
The results showed that:
- ALT flares occurred more frequently in HBeAg-positive patients than HBeAg-negative patients whatever the treatment assignment and they occurred predominantly during the first 24 weeks of the study.
- None of ALT flares occurring before Week 24 was associated with sign of hepatic decompensation (such as bilirubin elevations).
- There was a slight trend toward a higher percentage of ALT flares in telbivudine arm during this period but this was mainly related to mild-to moderate ALT flares.
- The Grade 3 or 4 ALT flares during the first 24 weeks of the study appeared to be correlated to high post baseline HBV DNA reductions (>4 log10 copies/ml or reduced to PCR-non detectable levels)
- Between the second period, from week 24 to week 52, ALT flares occurred predominantly in lamivudine treated patient whatever the HBeAg status. The number of patients under LdT therapy experiencing an ALT flares during this period remained low (n=4).
- Three patients in lamivudine group had severe ALT flares associated with bilirubin elevations during this period
- Overall, the majority of patients with grade 3 or 4 ALT flares occurring after the first six months of treatment failed to achieve PCR non- detectable HBV DNA levels or HbeAg loss at week 52 or had virologic breakthrough.

A time to onset of 4-5 weeks for the occurrence of on-treatment ALT flares was identified

From week 52 to week 76, the incidence of ALT flares was still higher in lamivudine recipients (3.9%) compared to telbivudine recipients (2.6%) but the difference tended to be reduced, mainly in HBeAg-positive patients. Two HBeAg-positive patient in telbivudine arm experienced ALT flares associated with bilirubin elevations, a marker of hepatic decompensation.

During the second year of treatment (week 52 to 104) based on November 11, 2006 cut-off, the rate of patients who experienced ALT flares (Grade 1-4) became lower in the telbivudine group compared to lamivudine group: 29 (6.5%) versus 39 (8.6%) in HBeAg positive patients and 5 (2.1 %) versus 20 (8.6 %) in HBeAg negative patients.

An analysis of the relationship between on-treatment ALT flares at year 2 and breakthrough/resistance in HBeAg positive patients indicates that:

- At year 2, approximately 19% (and 20%) of LdT-treated patients had resistance to telbivudine (or virological breakthrough) compared to 31% (and 33%) in the lamivudine group.
- Among patients who had resistance and/or virological breakthrough, an ALT flare was developed by approximately 23 -25% of LdT-treated patients compared to 15 -17% of lamivudine-treated patients.

Data derived from Study NV-02-010 support a higher incidence of ALT flares in lamivudine-treated patients and a small number of patients who developed these phenomena among patients receiving telbivudine. In the telbivudine monotherapy arm in this study, a total of 5 among 44 patients (11%) experienced ALT flares from baseline to Week 104 versus 6 patients among 19 in the lamivudine arm (31.5%). Overall, three patients discontinued study treatment due to ALT flares (2 LAM patient and 1 LdT patient).

After week 104, 5 out of 31 patients in the telbivudine arm (16.1%) versus 1 out of 7 patients in the lamivudine arm (14.3%) had an on-treatment ALT flares. None was associated with bilirubin elevations. Although the comparison should be made with particular caution due to the limited number of patients in lamivudine, these findings are overall in line with those observed from the Globe study i.e. there is a trend toward an increase in ALT flares in the HbeAg-positive patients receiving telbivudine during the second year of the study. This should be confirmed when the complete week 156 of study NV-02B-010 and complete week 104 of study NV-02B-007 will become available.

Off-treatment or post-treatment ALT flares were reported in 8 patients on telbivudine in studies NV-02B-007, NV-02B-003/010 compared to 5 patients in lamivudine group.

The telbivudine-treated patient with off-treatment ALT flare had a time-to onset of three months and a half. Due to the limited number of patients with off-treatment ALT flares, it remains difficult to estimate a delay for the occurrence of off-treatment ALT flares.

Overall, the majority of off-treatment and post-treatment ALT flares occurred in HbeAg-positive patients and were not associated with criteria of severity.

CK elevations:

A higher incidence of CK elevations in telbivudine-treated patients was consistently reported across studies and in particular in the pivotal study NV-02B-007.

Table 22: Patients(%) with new-onset Grade ½ and Grade ¾ CK elevations – NV-02B-007

	Lamivudine N=687	**Telbivudine N=680**
Baseline to Week 52:		
Grade 1-2	248 (36.1%)	410 (60.3%)
Grade 3-4	21 (3.1%)	51 (7.5%)
Baseline to Week 76*		
Grade 1-2	282 (41.0%)	436 (64.1%)
Grade 3-4	24 (3.5%)	69 (10.1%)

Post-week 52 to week 104*		
Grade 1-2	163 (23.7%)	373 (54.9%)
Grade 3-4	6 (0.9%)	42 (6.2%)

*From 120 day safety update

Patients were not excluded from participation in the pivotal study on the basis of elevated pre-treatment CK levels and 20.8% of patients in LAM group had baseline CK elevations compared to 23% in the telbivudine.

Although there was high inter and intra variability in baseline CK levels, the higher incidence and severity of CK elevations in telbivudine group observed in this study were of concern.

Table 23

CK Toxicity Grade[2]	**Telbivudine 600 mg n=680 (%)**	**Lamivudine 100 mg n=687 (%)**
Grade 1 (3.0-5.9 x ULN)	14.9	3.1
Grade 2 (6.0-9.9 x ULN)	5.8	1.2
Grade 3 (10.0-19.9 x ULN)	1.5	0.3
Grade 4 (>20 x ULN)	1.0	0.7
Discontinuation/Interruption due to CK	0.7*	0

[1] On-treatment value worsened from baseline to Grade 1 to 4 during therapy up to Week 52

[2] Grading system corresponds to the 2004 version of the DAIDS AE grading table

*Two patients on telbivudine had study drug interrupted, while three patients had study drug discontinued

Although a re-analysis of the Treatment-Emergent CK Abnormalities in Patients with Chronic Hepatitis B by Week 52 using the updated DAIDS Toxicity Scale defining Grade 1 to 4 for CK elevations (December 2004 instead 1992 in the initial application), showed that the number of Grade ¾ CK elevations appears less important in both treatment groups, the results confirmed that these events occurred more frequently in the telbivudine arm.

Data from supportive study NV-02B-003 support these findings with higher median CK levels at Week 52 in telbivudine arm or LdT+LAM combination arm. Post-week 104 to week 156 data from study NV-02B-010 were also in line with those previously discussed. Three patients in LdT arm versus none in LAM arm experienced a Grade 3-4 CK elevations after week 104 in this study (17 patients (38.6%) and 1 patient (3.3%) respectively for Grade 1-2 CK elevations). These are incomplete data precluding to draw final conclusion on the safety profile of telbivudine in the third year of therapy.

With respect to time to onset, these CK elevations occurred predominantly after six months of therapy and appeared to generally decrease spontaneously despite the treatment continuation. After 52 weeks, there was a slight decrease of incidence of CK increased followed by a stabilisation period up to week 104.

Based on baseline to week 52 data, Grade 3 or 4 CK elevations of 14% of patients in telbivudine arm were not resolved up to week 52 and 54.4% were only decreased to grade 1-2. This was confirmed by post week 52 data where 60% of telbivudine patients who experienced Grade 3-4 CK increase returned to Grade 1-2. Only 14% resolved to normal value.

With respect to clinical feature, the majority of patients with Grade 3-4 or Grade 1-2 CK elevations were asymptomatic with no particular clinical symptoms reported. However, fatigue appeared the more commonly reported adverse among patients experiencing CK increased. Moreover, arthralgia, back pain, myalgia and neck pain were all more frequently reported in patients with Grade 3 or 4 CK elevations than in patients without Grade 3-4 CK elevations. After week 52 to week 104, these findings were confirmed. Although CK elevations were often reported without any specific symptoms, there was one case of a possible telbivudine-induced-myopathy.

Another serious case of polymyositis attributed to telbivudine in study NV-02B-015 (Phase III in Chinese patients).

The possible mechanism behind CK elevations and muscular toxicity related to telbivudine has not been elucidated. According to data up to week 52 from the pivotal study, patients treated with telbivudine are at 2.29 times (95% CI, 1.34, 3.92) greater risk for Grade 3/4 CK elevations compared to those patients treated with lamivudine. A preliminary analysis of risk factors for Grade 3-4 creatine kinase elevations by logistic regression showed higher baseline CK, younger age, and non-Asian ethnicity were associated with a higher risk of a Grade 3/4 CK elevation. The influence of Caucasian race was observed however in both treatment groups.

With respect to class effects of nucleoside analogues, so far no case of lactic acidosis has been observed with telbivudine, only one patient in NV-02B-003 receiving telbivudine in combination with lamivudine discontinued the treatment due to possible drug-induced neuropathy of mild intensity and one serious adverse event of pancreatitis was reported in the telbivudine arm.

Patients in the telbivudine treatment group (n=55, 8.1%) and lamivudine treatment group (n=47, 6.8%) developed on-treatment adverse events that could represent manifestations of hypersensitivity reactions. In the telbivudine treatment arm, there were 72 (8.1% of patients) treatment-emergent adverse events that might have represented hypersensitivity reactions. The majority of these AEs manifested as rash (n=36) and urticaria (n=7).

A clinical pharmacology study (NV-02B-024) evaluated the effects of telbivudine at clinical (600 mg/day) and supra-therapeutic (1800 mg/day) telbivudine doses on cardiac safety. No safety concern has been identified.

- Other laboratory findings

Overall, mean change from baseline to Week 52 of all measured haematology parameters in study NV-02B-007 were limited and no noticeable differences between lamivudine and telbivudine treatment groups were observed.
Hematology parameters from study NV-02B-003 confirm the data of the pivotal study.

The clinical chemistries abnormalities are summarised in the table 24:

Table 24: Clinical chemistries - change from baseline to Week 52- Nv-02B-007

Laboratory test	Statistic	Lamivudine	Telbivudine
ALT	N	663	661
(IU/l)	mean (SE)	-113.3 (5.61)	-107.5 (4.41)
AST	N	663	661
(IU/l)	mean (SE)	-53.9 (2.8)	-45.9 (2.5)
Amylase	N	663	661
(U/l)	mean (SE)	-3.5 (2.1)	-2.3 (0.8)
Lipase	N	663	661
(U/l)	mean (SE)	1.0 (1.5)	-2.5 (0.8)
Creatinine	N	661	661
(mg/dl)	mean (SE)	-0.03 (0.01)	-0.08 (0.01)
Total bilirubin	N	660	661
(mg/dl)	mean (SE)	-0.02 (0.01)	0.02 (0.01)
Creatine kinase	N	663	661
(IU/l)	mean (SE)	52.2 (36.2)	195.0 (17.1)

In study NV-02B-007, 27.6% of telbivudine treated patients had grade 1-4 amylase elevations, and 21.5% had grade 1-4 lipase elevations. Of these, only a small percent were grade 3/4, namely 0.3% for amylase and 1.9% for lipase. A higher percent of patients in lamivudine group than telbivudine group reported grade 1-4 amylase elevations, 29% and grade 1-4 lipase elevations, 25.0%. Of the amylase elevations in lamivudine group, 0.4% were grade 3/4 and 3.8% of lipase elevations were grade ¾.

Elevations of amylase and lipase were not associated with clinical pancreatitis, except in one patient, in whom the mild pancreatitis was thought to be unrelated to treatment.

Grade 3 AST or ALT elevations were defined as > 3-10 x the baseline value and a grade 4 elevation as >10 x the baseline value. As requested by CHMP, the applicant reanalysed data on AST and ALT definitions using the AIDS table for grading severity of these laboratory values (i.e., Grade 3 is defined as >5 but <10 x ULN and Grade 4 is defined as >10 x ULN). These data showed that, from baseline to week 52, Grade ¾ ALT abnormalities (11.6% for LAM arm and 11.2% for LdT arm) and AST abnormalities (6.0% for LAM arm and 4.6% for LdT arm) were observed in similar frequency in both treatment groups.

- Safety in special populations

There are no safety data pertaining to the use of telbivudine neither in paediatric nor in elderly. This is adequately reflected in the SPC.

In patients with renal impairment no specific safety concerns emerged attributed to telbivudine.

In patients with hepatic, impairment, no specific safety concerns emerged.

The safety of telbivudine in patients with decompensated liver disease is currently unknown as well as in HIV co-infected patients, and liver transplant recipients.

- Pregnancy

Twenty pregnancies have been reported in female patients in the clinical trials (12 patients were included in the pivotal study NV-02B-007) and 24 pregnancies have been reported in partners of male patients (15 from pivotal study). From the exposed pregnancies for which an outcome is available, no pregnancy in the telbivudine groups has resulted in a congenital abnormality. No conclusion can be drawn on the safety of telbivudine in pregnant female patients or in partners of male patients based on the available data.

- Safety related to drug-drug interactions and other interactions

An analysis of adverse events for the most commonly prescribed concomitant medications reported in patients taking these medications in study NV-02B-007 did not raise any particular concern.

- Discontinuation due to adverse events

In study NV-02B-007, the incidence of treatment discontinuation due to AEs was low and comparable between both telbivudine and lamivudine treatment group (2.8% in each group); the most common AE leading to discontinuation or interruption in the LdT group was blood creatine phophokinase increased with a total of five patients who stopped study drug due to this adverse event.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 28: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risk		
Myopathy	cumulative analysis of reports of myopathy PSUR In ongoing and planned future studies assessment of correlation between CK and muscular effects associated	Warning in the SPC for close monitoring of muscle related adverse events A proposal for an educational material to physicians to enhance the understanding of identified risks of muscular effects (CK elevations and myopathy) will be submitted to the CHMP for consideration
Symptomatic CK elevation	Proposal for investigation of the mechanism of clinical CK elevations using non-clinical testing models	Idem
Potential risks		
ALT flares – post-treatment	- cumulative analysis of reports of post-treatment ALT flares reported in PSUR In ongoing, future selected planned studies, and future post marketing studies, post-treatment ALT flares will be monitored.	Warning in the SPC to monitor hepatic function at regular interval with both clinical and laboratory follow-up for at least 6 months after discontinuation of treatment.
Lactic acidosis with hepatic steatosis without hepatic steatosis	• PSUR - cumulative analysis of reports of lactic acidosis • In ongoing, future selected planned studies, and future post marketing studies, lactic acidosis will be monitored.	Class labelling warning in SPC
Neuropathy	• PSUR - cumulative analysis of reports of neuropathy	
Pancreatitis	• PSUR - cumulative analysis of reports of pancreatitis .	
Resistance	• Annual reports on resistance from main ongoing/planned clinical studies • Annual reports on phenotypic testing and cross resistance testing against well characterised single agent mutations that confer resistance to established and new HBV therapeutic agents	
Hypersensitivity reactions	cumulative analysis of reports of hypersensitivity reported in PSUR.	Rash listed in section 4.8 of SPC
Pregnancy	Registration of telbivudine in the Antiretroviral Pregnancy Registry reports on a semiannual basis attached to the PSUR	

The CHMP, having considered the data submitted in the application was of the opinion that, beyond those included in the product information, there is no need for further risk minimisation activity for the safe and effective use of the medicinal product. However the need for an educational material to physicians to enhance the understanding of identified risks of muscular effects (CK elevations and myopathy) as proposed by the applicant will be considered as part of the follow-up measures to be fulfilled post-authorisation.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a few minor unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. These will be addressed as part of the follow-up measures to be addressed post-authorisation.

Non-clinical pharmacology and toxicology

Telbivudine is a nucleoside analogue with activity against HBV polymerase. Telbivudine showed an antiviral activity in in vitro and in vivo models compatible with clinical use for the treatment of hepatitis B. Safety pharmacology studies did not reveal any effect of telbivudine on cardiovascular, respiratory and central nervous systems.

The toxico-pharmacokinetics of telbivudine has been adequately studied. At high oral doses, toxicokinetic results showed a non-linear relationship between the dose and the exposure suggesting that it would have been difficult to obtain animal exposures higher than the one obtained in the studies. From a pharmacokinetic point of view the results from non-clinical studies may therefore be considered valuable.

The toxicity of telbivudine was correctly evaluated in standard toxicological studies. Telbivudine produced little or no toxicity and no target organ could be clearly identified. Telbivudine was not genotoxic in appropriate models and telbivudine did not show any carcinogenic potential.

Telbivudine crossed the placenta in rats and was found in milk of lactating animals. No evidence of a direct toxic effect of telbivudine was seen in standard tests of reproduction toxicology. Considering these data and the lack of data in pregnant women and on excretion in human milk, the SPC recommends that telbivudine should not be used during pregnancy unless clearly necessary and that women should not breastfeed.

Telbivudine did not induce cytotoxicity; myelosuppression, mitochondrial toxicity have all produced negative results. Additionally, LdT triphosphate was shown to have low affinity for human DNA polymerase α, β and γ.

Telbivudine represents a low environmental risk.

Efficacy

The pharmacokinetics profile of telbivudine is characterised by a rapid absorption, low binding to plasma proteins, excretion primarily via renal route. There is no food effect on telbivudine bioavailability and therefore telbivudine can be taken regardless of food intake. Although the pharmacokinetics profile of telbivudine in hepatitis B infected patients does not seem to differ from healthy volunteers, patients did not receive the recommended dose. Further data will therefore be provided post-authorisation to further substantiate the steady state pharmacokinetics in patients.

Because telbivudine is primarily renally excreted unchanged, renal impairment may increase telbivudine exposure. Therefore for patients with moderate (creatinine clearance 30-49 ml/min) or severe renal impairment (Crcl< 30 (not requiring dialysis) or end stage renal disease), dose adjustment through extending dosing interval is necessary as reflected in the SPC. Because the recommendations are not based on results from patients with impaired renal function receiving 600 mg dose, a warning has been included in the SPC to closely monitor virological response in patients with renal impairment receiving telbivudine with increased dosage interval. The applicant committed to pursue its exploration for a daily dose adjustment with an oral solution under development. No dosage adjustment is necessary for patients with hepatic impairment. The use of telbivudine in patients with hepatic impairment will be further substantiated by the planned phase III study in patients with decompensated liver disease, the results of which will be provided post-authorization.

Since telbivudine is not a substrate, inducer and inhibitor of CYP450 isoenzymes or other transported, the interaction potential is low. No interaction was observed with lamivudine, adefovir, tenofovir and an experimental nucleoside analogue (valtorcitabine) all excreted renally via active tubular secretion, nonetheless it cannot be excluded that there may be interaction with other substances undergoing active renal secretion as highlighted in the SPC. Although no significant interaction was evidenced between telbivudine and pegylated interferon-alfa 2a, the high inter-individual variability of the pegylated interferon pharmacokinetics makes it difficult to draw definitive conclusion in this field and further data derived from the clinical study investigating the combination therapy will be provided post-authorisation. Although there was no significant interaction between telbivudine and cyclosporin, given the potential toxicity of telbivudine and cyclosporin on the muscle, a warning has been included in the SPC.

The choice of the 600 mg dose recommendation based on dose finding studies and modeling is considered acceptable.

Although the clinical programme has been initiated prior to the CHMP guideline on anti-hepatitis B therapy, it is in line with the spirit of the guideline.

The demonstration of the efficacy of telbivudine relies mainly on study NV-02-B007 (also called Globe) an ongoing 104-week, phase III, randomised, double-blind, multicentre, international clinical trial designed to compare the efficacy and safety of telbivudine (600 mg/day) to lamivudine (100 mg/day). This study is performed in adult patients with chronic hepatitis B and compensated liver disease who had no prior nucleoside/nucleotide analogue therapy and had received no interferon alfa or other immunomodulators for at least one year.

The study included both HBeAg positive and HBeAg negative patients, which are now considered as 2 distinct disease entities, but a stratification by HBeAg status was planned and study results were finally analysed separately in each population subgroups. The randomisation was also stratified by ALT level (< or > 2.5XULN) known to have an impact on treatment response.

Week 52 results on the primary combined endpoint [virological (HBV DNA < 5 log10 copies/ml) and serological (HBeAg loss) or biochemical response (ALT normalisation)] demonstrated:

- the superiority of telbivudine treatment in the HBeAg-positive group (ITT analysis 75.3 % versus 67 % CI95.68% = [2.4% ; 14.2%], p=0.0047 and EE analysis 77 % versus 67.1 % CI95.68% = [4.0% ; 15.8%], p=0.007)
- -and the non-inferiority (point estimate in favour of telbivudine) of telbivudine treatment in the HBeAg negative group compared to lamivudine treatment (ITT analysis 75.2 % versus 77.2% CI95.68% = [-10.2% ; 6.1%], p=0.6187 and EE analysis 76.3 % versus 80.8 % CI95.68% = [-12.1% ; 3.3%], p=0.2461).

With respect to the main secondary endpoint, histological response defined as $\geq$ 2 point decrease in the Knodell Necroinflammatory score from baseline with no worsening of the Knodell Fibrosis score, telbivudine was superior to lamivudine in HBeAg positive patients (71% versus 61%) and non-inferior in HBeAg negative patients (71 % versus 70 %).

When considering the other secondary efficacy endpoints (virological, biochemical and histological), consistent results were observed through the analyses that demonstrated either the non-inferiority of telbivudine versus lamivudine or the superiority of telbivudine at week 52.

The re-analysis of the efficacy data using the endpoint recommended in the CHMP Guideline confirmed the results. Nonetheless the superiority of telbivudine did not translate into higher seroconversion in HBeAg positive patients. Baseline ALT> 2ULN and baseline HBVDNA < 9 log copies/ml were associated with higher rates of seroconversion.

Preliminary 104 weeks results showed that telbivudine treated patients exhibited higher degree of maintained responses on all the key efficacy measures examined in both HBeAg positive and negative patient populations.

The population enrolled in this study mainly consists of Asian patients. The European/Caucasian population was limited (98 patients exposed to telbivudine). Based on the pharmacokinetic/pharmacodynamic analyses of the drug, telbivudine did not display ethnic sensitivity according to the ICH-E5 guideline on foreign data. However there was a concern that in the sub-group of European/Caucasian HBe Ag negative patients the efficacy results suggested that it would be better for these patients to receive lamivudine than telbivudine. In addition the CHMP considered that the limited number of European/Caucasian patients was a concern as regard to the under-representativity of "European" genotypes such as A. Additional 104 weeks results showed that the trend towards a lower therapeutic response observed in the 52 weeks report in the sub-group of Hbe Ag negative Caucasian patients was no longer apparent. In line with the results on the overall population, the apparent superiority of telbivudine over lamivudine became also true in this sub-group. Such a change was mainly driven by the results on ALT normalisation.

Although such a concern was solved, it remained that the data to support the use of telbivudine in European/Caucasian patients were limited at this stage. The population enrolled was mostly of Asian origin and the "European" HBV genotypes were under-represented (most commonly HBV genotypes were B (26%) and C (51%)). The applicant was therefore requested to further substantiate the efficacy of telbivudine in Caucasians/Europeans by conducting a clinical study, for which the proposed design is to be validated by the CHMP before the study initiation.

The study enrolled only a limited number of patients with cirrhosis (6 %) and therefore adequate warnings for the use of telbivudine in these patients have been introduced in the Summary of Product Characteristics.

With respect to resistance in vitro data and data from the main study identified M204I mutation as the key determinant behind telbivudine resistance. Cross-resistance has been observed with anti-HBV nucleoside analogue. Virological breakthrough (confirmed > 1 log 10 copies/ml increase from nadir PCR assay at week 48) accounted for 5.9 % in telbivudine versus 15.3 % in lamivudine group in HBeAg positive and 2.3 % versus 12.5 % in HBeAg negative respectively. HBV resistance at week 48 accounted for 5 % for telbivudine versus 1 % for lamivudine in HBeAg positive and 2.3 % and 11.2 % in HBeAg negative patients respectively. The applicant undertook to provide further resistance/cross-resistance data as part of the follow-up measures to be fulfilled post-authorisation.

The optimal treatment duration is currently unknown. Patients who achieved HBV DNA < 3 logs copies/ml by week 24 had optimal responses to treatment. The applicant committed to provide additional data from ongoing/planned studies, as part of the follow-up measures to be fulfilled post-authorisation, looking particularly at the some efficacy issues such as baseline predictors of favourable response, baseline predictor of HBeAg seroconversion, predictive efficacy outcome by HBV DNA level at week 24 to detect suboptimal responders, durability of HBeAg-seroconverters off treatment.
Currently the demonstration of efficacy of telbivudine is limited to HBeAg positive and negative adult patients with chronic hepatitis B and compensated liver disease. To address for the deficiencies of the evaluation of efficacy of telbivudine in wide range of populations as recommended in the CHMP Guideline, the applicant committed to provide post-authorisation results of planned or ongoing studies in other populations such as HIV-HCV co-infected, patients with decompensated liver disease.

In addition in order to better evaluate the optimal use of telbivudine, the applicant will provide post-authorisation studies looking at comparing its efficacy with newer anti-HBV treatment (e.g adefovir dipivoxil and entecavir) at its use in combination therapy (e.g adefovir, lamivudine, pegylated interferon alfa2a) and switching from lamivudine to telbivudine.

There are currently no data to support the use of telbivudine in children but the applicant undertook to complete the development programme in this population.

Although the significance of quantitative cccDNA levels in the liver has not been established, results from a planned cccDNA analysis from a subset of patients from study NV-02B-007 will be submitted as part of follow-up measure to be fulfilled post-authorisation.

Safety

Safety analyses are based on data on over 1,500 patients who have received the recommended dose of telbivudine. The main data derived from study NV-02B-007 and the majority of patients are Asian and HBeAg-positive male patients. Caucasian subjects represent only 15% of the key study population**.**
The most commonly adverse reactions associated with telbivudine reported in Globe study were blood creatine phosphokinase increased, fatigue, headache, nausea, dizziness, diarrhoea, rash, ALAT/ASAT increased, blood amylase and lipase increased.

Caucasian patients and other ethnicities were more at risk to develop adverse events and serious adverse events than Asian patients, especially fatigue, headache and blood creatine kinase (CK) elevations.

With respect to CK elevations: Grade 1-2 and Grade 3-4 CK increased were reported in 60.1% and 7.5% of patients in the telbivudine arm versus 36.1% and 3.1% in the lamivudine arm from baseline to week 52. Complete week 76 data and interim week 104 data supported these observations. These CK elevations occurred predominantly after six months of therapy and appeared to generally decrease spontaneously despite the treatment continuation. However, up to week 52, a percentage of 14% with Grade 3-4 CK elevations did not resolve at the time of the last visit recorded. After week 52, there was a trend toward a stabilisation of incidence of CK elevations. There is a lack of association between a CK elevation and specific clinical symptoms. High baseline CK level and Caucasian race were identified as potential predictor of CK grade 3 or 4 elevations. A warning has been included in the SCP to recommend a close monitoring of muscle related adverse events and the applicant committed to further investigate the mechanism behind CK elevations.

With respect to ALT flares, on-treatment ALT flares were observed less frequently in telbivudine-treated subjects (10.3%) compared with lamivudine-treated subjects (13.1%). These on-treatment ALT flares occurred more frequently in HBeAg-positive patients than HBeAg-negative patients whatever the treatment assignment and they occurred predominantly during the first 24 weeks of the study. Before week 24, they appeared to be correlated to high post baseline HBV DNA reductions and no sign of hepatic decompensation was reported. During the 2nd year of treatment, (week 52-0104), 29 (6.5 %) telbivudine treated HBeAg positive patients experienced ALT flares (Grade 1-4) compared to 39 (8.6 %) with lamivudine. For HBeAg negative patients these figures accounted for 5 (2.1%) versus 20 (8.6%) respectively. Virological breakthrough was associated with a slightly greater proportion of ALT flares in telbivudine treated patients compared to lamivudine.

The number of patients who experienced off-treatment and post-treatment ALT flares is too limited to draw any conclusion however a warning on the monitoring of the hepatic function after stopping treatment has been included.

Regarding pregnancy, given the potential for foetal exposure the applicant committed to register telbivudine into the Antiretroviral pregnancy registry to identify proactively the safety profile of telbivudine in pregnancy.

Even the safety database adverse reactions reported with telbivudine in the clinical trials have been included in the Summary of Product Characteristics.
All the information has been appropriately translated into the package leaflet for which a user test has been adequately performed.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.1 adequately addressed these.

Risk-benefit assessment

The clinical experience is limited to nucleosi(ti)de-naïve HBeAg positive and negative adult patients with compensated liver disease, mostly patients of Asians origin and infected with HBV genotypes B and C.

Based on the clinical efficacy, safety and resistance data of telbivudine, which were overall superior in HBeAg positive and comparable in HBeAg negative patients to lamivudine, the benefit risk ratio of telbivudine is considered positive. As the experience in Caucasian is very limited, the applicant committed to conduct a study comparing telbivudine to adefovir in HBeAg-negative Caucasian patients to reinforce the benefit/risk in this population. In addition the applicant committed to provide additional data post-authorisation to address a number of clinical questions related to the use of telbivudine in the management of hepatitis B infected patients (e.g baseline predictors of favourable response, combination therapy, durability, resistance emergence) and in certain populations (e.g. HIV/HBO co-infected patients, decompensated patients, children). The chronic nature of hepatitis B virus therapy and long-term disease outcomes are such that clinical trials do not fully address long-term risk of HBV therapy. A Risk Management Plan was submitted and includes agreed pharmacovigilance activities in addition to the use of routine pharmacovigilance to investigate further some of the safety concerns. The main safety concern associated with telbivudine is creatine phosphokinase elevations requiring a close monitoring of muscle related adverse events as recommended in the SPC.

Due to the nature of the disease, telbivudine therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Sebivo was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

> "treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. See section 5.1 *of the Summary of Product Characteristics* for details of the study and specific patient characteristics on which this indication is based."