Sponsor
Novartis Farmacéutica, S.A

Generic Drug Name
Telbivudine

Therapeutic Area of Trial
Antiviral for systemic use

Approved Indication
Treatment of chronic hepatitis B (CHB) in adult patients with compensated liver disease and signs of viral replication, serum levels of alanine aminotransferase (ALT) persistently elevated and histological signs of active inflammation and/or fibrosis.

Study Number
CLDT600AES01

Title
Exploratory prospective study to describe hepatitis B viral kinetics in naïve and non-naïve patients during the first 24 weeks of treatment with telbivudine. EBEREST study.

Phase of Development
Phase IIIB / IV

Study Start/End Dates
3 March 2008 to 29 December 2009

Study Design/Methodology
This is an exploratory prospective, open, multicenter study, to describe the HBV kinetics during the first 24 weeks of treatment with telbivudine in two independent groups of negative HBeAg patients with CHB. Treatment groups are defined as:

- Naïve patients: They received 600 mg oral telbivudine monotherapy (group A).
- Non-naïve patients with suboptimal primary response or secondary virological reactivation after prior treatment with adefovir: combination therapy of 600mg telbivudine plus 100mg oral adefovir (group B).

A subgroup of patients that finally involved only three patients in group A was defined. Among this group named as “group a” a detailed viral kinetics for the first 4 weeks of treatment was done.

Centers
16 centers in Spain

Publication
Not applicable

Objectives

Primary outcome/efficacy objective(s)

- To describe the HBV kinetics during the first 24 weeks of treatment with telbivudine in naïve patients (never received antiviral treatment with nucleos(t)ids) and non-naïve patients (patients who had received prior adefovir treatment with suboptimal primary response or secondary virological reactivation).

Secondary outcome/efficacy objective(s)

- To describe the virus dynamics in the first 4 weeks of treatment with telbivudine, in a subgroup of naïve patients and in other non-naïve group with suboptimal primary response or secondary virological reactivation.
- The qualitative comparison of the viral kinetics patterns in naïve and non-naïve patients.

- To evaluate the differences in viral kinetics according to baseline viral load and viral genotype.
- Percentage of patients with undetectable DNA-HBV (<300 copies / ml or equivalent at different time intervals).
- Rate of resistance development until week 24.
- Percentage of patients with normal ALT at week 24 and its relationship with inhibition of HBV replication.
- To quantify the levels of HBsAg in naïve and non-naïve patients to the initiation of treatment and at 24 weeks.
- To evaluate the association of different viral kinetic patterns in the first 24 weeks of treatment and response patterns over the longer term defined in the GLOBE study.
- To validate a qualitative therapeutic adherence test easy to use (Morisky-green) in patients with CHB.

Test Product (s), Dose(s), and Mode(s) of Administration
TELBIVUDINE
Pharmaceutical form: film-coated tablets 600 mg
Route of administration: oral
Concentration: 600.0 mg / tablet
Dosage: 600 mg once daily

Reference Product(s), Dose(s), and Mode(s) of Administration
10 mg oral adefovir combined with 600 mg telbivudine

Criteria for Evaluation
Primary outcome: Efficacy
Primary:
The efficacy assessments were made by:
1-Determination of serum HBV DNA tested using TaqManTM Cobas HBV assay. The extraction of serum samples for determination of HBV DNA during the selection was made according to criteria of biochemical and virological laboratory in their respective local centers within 8 weeks before the start of treatment, to determine eligibility for the study and in the remaining study visits to assess the impact of treatment.

Secondary:
1- Determination of ALT levels from serum samples extracted in all study visits.
2- Determination of HBsAg levels in samples extracted in the study visits.
3- Evaluation of monthly adherence using a direct method, the accounting for the medication taken by patients, and an indirect method, the qualitative Morisky-Green questionnaire.

Secondary outcome: Safety
The safety endpoints were determined from the records of all adverse events, serious adverse events, complete physical examination, regular assessment of vital signs and evaluation of blood laboratory results.

Pharmacology:
Not applicable
Other:
Not applicable

Analysis Population
ITT-I Population
Included all patients enrolled in the study, who had received at least one dose of study medication and had baseline and week 24 serum HBV DNA available assessments to carry out the primary analysis.

Safety population
Included all patients who received at least one dose of study medication. Patients were analyzed according to treatment received during the study. It should be noted that a clinic visit to a patient who did not present adverse events was also a safety assessment.

Per Protocol
Included all patients that met all selection criteria, who had taken the study medication according to protocol and had the baseline and 24 weeks serum HBV DNA assessments to carry out the primary analysis.

Statistical Methods
Exploratory Analysis

Primary efficacy endpoint
The primary endpoint was defined as the change of HBV DNA at 24 weeks compared to baseline (visit 2) of the values given by the central laboratory. HBV DNA baseline was defined as the last one made before taking the first dose. The determination of HBV DNA was performed according to HBV DNA levels in log scale 10 copies / ml.

Secondary efficacy endpoints
1. To evaluate the change of HBV DNA between each post baseline visit versus baseline (Visit 2) of the values given by the central laboratory.
2. To describe viral dynamics in the first 4 weeks of treatment in a subgroup of patients treated with telbivudine in naïve and not naïve patients.
3. To evaluate the differences in viral kinetics according to baseline viral load and viral genotype.
4. Percentage of patients with undetectable HBV DNA (<300 copies / ml) or equivalent (see Annex VII of the protocol)) at different time intervals
5. Rate of emergence of resistance to week 24.
6. Percentage of patients with normal ALT at week 24 and its relationship with inhibition of HBV replication.
7. To quantify the levels of HBsAg in naïve and not naïve patients at different time intervals.
8. To evaluate the association of different viral kinetic patterns in the first 24 weeks of treatment and response patterns over the longer term defined in the GLOBE study.
9. Compliance with treatment according to Morisky-Green.
10. Adherence to treatment by pill count.

Safety
The safety analysis was based on the safety population: all patients who received at least one dose of treatment.
The adverse events (AEs) reported after the initiation of treatment with telbivudine or adefovir combination therapy plus telbivudine were coded using the medical dictionary MedDRA version 12.1. Frequencies of adverse events (AEs) were calculated per system / organ (SOC) and Preferred Term (PT). Incidence and type of AA were summarized. The AA

reported as "suspected" in relation to study medication were considered related to study medication. When the classification on the relationship of the medication with the study was missing it was considered related to the study medication. Also it was calculated the AE frequencies related to the medication. A list of AE patients was generated that showed the details contained in the Case Report Form (CRF).
Vital signs were described: weight, height, blood pressure and pulse rate per visit (Visit 1, visit 2, visit 6 and visit 9).
It was described the number of patients who had shown abnormalities in the different systems examined: general appearance, skin, throat, lungs, heart, abdomen, lymph nodes or other per visit (visit 1, visit 6 and visit 9).
Laboratory descriptively data for all parameters listed and for visit were presented. On the other hand, the number of patients by parameter and visits that have shown abnormalities were described.
All concomitant medications and therapies taken during the course of the study were recorded in the CRF and were coded using the WHO Drug Dictionary (version 2009). These medications are described by the number of patients affected and total percentage of patients.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

1. Male or female, of at least 18 years old.
2. CHB documented, as defined by all the following criteria according to the standard clinical practice in the 6 months prior to its inclusion in the study:
   - Clinical history compatible with CHB.
   - Positive HBsAg.
   - Negative HBeAg.
   - History of chronic liver inflammation evidence, documented by previous history of elevated serum ALT with or without histological documentation as previous liver biopsy performed at any time prior to its inclusion in the study and documented.
   - Concentration of ALT in serum:
     - Naïve patient: elevated ALT (1,3 - 10 x the upper limit of normal (ULN)) at the screening visit.
     - Non-naïve patient: may have elevated ALT (1,3 - 10 x ULN) or normal.
   - Concentration of serum HBV DNA determined in the local laboratory according to clinical practice and equivalent to:
     - Naïve patient:> 4 log10 copies / mL as determined by the COBAS Amplicor test or equivalent.
     - Non-naïve patient: $\geq$ 3 log10 copies / mL after a minimum of 24 weeks of treatment as determined by the COBAS Amplicor test or equivalent.
3. Patient willing and able to comply with the study drug and all other requirements of the study.
4. Patients that could participate in the study and who consent to participate after they have been clearly explained the purpose and nature of the investigation.

Exclusion criteria:

1. History of hypersensitivity to any study medications or drugs with similar chemical structures or their excipients.
2. Coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV).
3. In relation to previous treatment, patients who have received Pegylated Interferon or any

immunomodulatory treatment will be considered naïve to nucleosids (t) and therefore will not be excluded from the study. Previous treatments that will be reason for exclusion include:

- Naïve patient: pre-treatment with lamivudine, adefovir, entecavir or other nucleoside analogues nucleosid (t) in research.
- Non-naïve patient: pre-treatment with lamivudine.

4. The patient has any of the following situations:
   - A history or signs / symptoms of hepatic decompensation clinical as ascites, esophageal variceal bleeding, hepatic encephalopathy or spontaneous bacterial peritonitis.
   - History of malignant disease of any organ system, treated or untreated for the past five years, without signs of local recurrence or metastases, with the exception of localized cutaneous basal cell carcinoma. In patients with previous results suggesting the possible existence of a hepatocellular carcinoma (HCC), the disease should be ruled out before placing the patient in the study.
   - One or more additional primary or secondary causes of liver disease known, other than Hepatitis B, including steatohepatitis. Note: Gilbert's syndrome and Dubin-Johnson syndrome are not considered exclusion criteria in this study.
   - History of clinical and laboratory signs of chronic pancreatitis, or demonstration of a clinical and analytical evolution that matches with a current pancreatitis.
   - History of disease that requires frequent or continued use of systemic corticosteroids, although inhaled corticosteroids are allowed.
   - The subject has a history of myopathy, myositis, or persistent muscle weakness.
   - In the opinion of the investigator have any other medical or social disorder that would prevent concurrent compliance with the testing program protocol, or may confuse the observations of efficacy or safety of the study. Or if in the opinion of the investigator the patient is at risk of developing serious neuropsychiatric illness or life threatening.
5. Any of the following laboratory values during the selection
   - Hemoglobin (HgB) <11 g / dL for men or <10 g / dL for women
   - Leukocytes total count (WBC) <3,000/mm3
   - Platelet count <70,000/mm3
   - Serum albumin <3.0 g / dL
   - Total bilirubin ≥ 3,0 mg / dL
   - Prothrombin time <65% despite administration of vitamin K
   - Serum creatinine renal function > 1.5 mg / dl
   - AFP (alpha fetoprotein)> 50 ng / mL
6. If a patient is pregnant or breastfeeding. Women of childbearing age should get a β-human chorionic gonadotropin (HCG) negative result in serum during the selection and should be agree to use effective contraception during the trial and for the six weeks following discontinuation of study medication, even in cases of infertility history.
7. The patient is participating in another clinical trial or has participated in the 3 months prior to inclusion in this study.
8. The patient is receiving or has received a drug not registered in the 3 months prior to inclusion in this study.

General Amendments to the protocol which affected inclusion/exclusion criteria:

Amendment no 1 (04/12/07):

The reason for the amendment was to address the request of the FDA to establish guidelines for the management of all subjects participating in telbivudine clinical trials and who complain of muscle weakness, muscle pain or myalgia, or fatigue related to effort. Complaints have been reported on muscle weakness, muscle pain or myalgia, or fatigue related to effort with the use of telbivudine therapy and the use of other therapies with nucleoside analogues. The method used to treat these events in the trial CLDT600AES01 has been the muscle symptoms algorithm described in the protocol as paragraph 3.7.1.1. All subjects whose follow-up was performed with this algorithm must be submitted to a physical examination with muscle strength test and answer the Muscular Symptom Questionnaire at each visit.
It also included the correction of small spelling errors detected in the study protocol.

Amendment no 2 (08/07/08):

The reason for the amendment was to address the following changes to the study protocol:

- Extension in the recruitment period initially planned to develop the protocol.
- Clarification of the assessment scheme visits
- Correction of typographical errors.

The inclusion period originally assigned to the protocol was not enough. The inclusion rate was not as expected due to the lack of patients for treatment with the typology required. Therefore, for the proper execution of the protocol and to achieve the pursued objectives, it was considered necessary to extend the enrollment period. It was removed the "Duration of the study" found in "Summary of protocol" section.
It was reassigned several symbols in the assessment visit schemes because they were incorrectly used. This helped understanding which determinations were made at the central laboratory.

Amendment no 3 (27/01/09):

The reason for the amendment was to address the following changes to the study protocol:

- Expansion of the inclusion / exclusion study criteria
- Change in Annex I, administrative procedures
- Correction of typographical errors
- Candidates to offer their informed consent

Due to the low rate of study recruitment and after a meeting with participant investigators, it was decided to extend some of the inclusion / exclusion criteria in order to best fit those used in clinical practice. Thus, to approach to the real patient profile and to achieve the objectives pursued in this protocol.
Note that for this study it was taken into account the exclusion criteria for a Phase II, instead of a phase IIIB-IV. And changes suggested do not put into risk at any time the safety of patients who participated in the study.

With regard to obtaining informed consent, it was noted that this protocol does not consider

the inclusion of patients who could not personally give consent and must be helped by a legal representative.

Patients disposition

	Group A	Group B	Total
Safety population n	27	3	30
Completed n (%)	21 (77.8)	2 (66.7)	23 (76.7)
Withdrawn n (%)	6 (22.2)	1 (33.3)	7 (23.3)
ITT II population n (%)	25 (92.6)	2 (66.7)	27 (90.0)
ITT I population n (%)	22 (81.4)	2 (66.7)	24 (80.0)
Per-Protocol Population n (%)	13 (48.1)	1 (33.3)	14 (46.7)

Demographic and clinical data

The following three tables show the demographic and clinical characteristics at screening visit in the ITT-I population / Safety population (n=24 / n=30).

		ITT Population HBV-DNA 24 weeks			Safety Population		
		Naïve	No Naïve	Total	Naïve	No Naïve	Total
Age (years)	N	22	2	24	27	3	30
	NMiss	0	0	0	0	0	0
	Mean (SD)	41.0 (10.5)	43.5 (0.7)	41.3 (10.0)	39.4 (11.0)	48.3 (8.4)	40.3 (11.0)
	95% CI	(36.4. 45.7)	(37.1. 49.9)	(37.0. 45.5)	(35.1. 43.7)	(27.5. 69.2)	(36.2. 44.4)
	Median	39.0	43.5	39.5	39.0	44.0	39.0
	(Q1,Q3)	(36.0. 45.0)	(43.0. 44.0)	(36.5. 45.0)	(33.0. 45.0)	(43.0. 58.0)	(36.0. 45.0)
	(Min,Max)	(18. 58)	(43. 44)	(18. 58)	(18. 58)	(43. 58)	(18. 58)
Sex	Males	17 (77.27%)	2 (100.00%)	19 (79.17%)	21 (77.78%)	3 (100.00%)	24 (80.00%)
	Females	5 (22.73%)	0 (0.00%)	5 (20.83%)	6 (22.22%)	0 (0.00%)	6 (20.00%)
Ethnic group	Caucasian	19 (86.36%)	2 (100.00%)	21 (87.50%)	22 (81.48%)	3 (100.00%)	25 (83.33%)
	Asian	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Black	2 (9.09%)	0 (0.00%)	2 (8.33%)	3 (11.11%)	0 (0.00%)	3 (10.00%)
	Hispanic	1 (4.55%)	0 (0.00%)	1 (4.17%)	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Arabian	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Other	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

		ITT Population HBV-DNA 24 weeks			Safety Population		
		Naïve	**No Naïve**	**Total**	**Naïve**	**No Naïve**	**Total**
Height (cm.)	N	21	2	23	26	3	29
	NMiss	1	0	1	1	0	1
	Mean (SD)	169.0 (8.8)	180.0 (5.7)	169.9 (9.0)	168.8 (9.5)	174.7 (10.1)	169.4 (9.5)
	95% CI	(165.0, 172.9)	(129.2, 230.8)	(166.0, 173.8)	(165.0, 172.6)	(149.7, 199.7)	(165.8, 173.0)
	Median	170.0	180.0	171.0	170.0	176.0	170.0
	(Q1,Q3)	(166.0, 175.0)	(176.0, 184.0)	(166.0, 176.0)	(162.0, 176.0)	(164.0, 184.0)	(164.0, 176.0)
	(Min,Max)	(144, 181)	(176, 184)	(144, 184)	(144, 185)	(164, 184)	(144, 185)
BMI (kg/m^2)	N	21	2	23	25	3	28
	NMiss	1	0	1	2	0	2
	Mean (SD)	26.6 (4.5)	27.8 (5.5)	26.7 (4.5)	26.4 (4.5)	30.6 (6.2)	26.8 (4.7)
	95% CI	(24.5, 28.6)	(-21.2, 76.8)	(24.7, 28.6)	(24.6, 28.2)	(15.2, 46.0)	(25.0, 28.7)
	Median	25.5	27.8	25.5	25.5	31.7	25.9
	(Q1,Q3)	(23,9, 30,4)	(24,0, 31,7)	(23,9, 30,7)	(23,1, 30,4)	(24,0, 36,2)	(23,5, 30,8)
	(Min,Max)	(20, 35)	(24, 32)	(20, 35)	(20, 35)	(24, 36)	(20, 36)
Weight (Kg.)	N	21	2	23	25	3	28
	NMiss	1	0	1	2	0	2
	Mean (SD)	76.2 (16.5)	90.7 (23.3)	77.5 (17.1)	75.4 (17.0)	92.9 (16.9)	77.3 (17.5)
	95% CI	(68.7, 83.8)	(-119.0, 300.4)	(70.1, 84.9)	(68.4, 82.4)	(50.8, 135.0)	(70.5, 84.1)
	Median	74.0	90.7	74.0	74.0	97.4	74.1
	(Q1,Q3)	(64.1, 89.0)	(74.2, 107.2)	(64.1, 90.0)	(62.0, 89.0)	(74.2, 107.2)	(63.1, 91.0)
	(Min,Max)	(51, 115)	(74, 107)	(51, 115)	(51, 115)	(74, 107)	(51, 115)

		ITT Population HBV-DNA 24 weeks			Safety Population		
		Naïve	**No Naïve**	**Total**	**Naïve**	**No Naïve**	**Total**
Time from diagnosis (years)	N	22	2	24	27	3	30
	Missing	0	0	0	0	0	0
	Mean (SD)	8.5 (9.5)	8.1 (5.7)	8.5 (9.1)	7.8 (8.8)	8.9 (4.3)	7.9 (8.4)
	95% CI	(4.3, 12.7)	(-43.0, 59.2)	(4.6, 12.3)	(4.3, 11.3)	(-1.7, 19.5)	(4.7, 11.0)
	Median	2.3	8.1	3.2	2.3	10.5	3.6
	(Q1, Q3)	(1.2, 16.6)	(4.1, 12.1)	(1.3, 16.2)	(1.0, 15.8)	(4.1, 12.1)	(1.2, 14.5)
	(Min, Max)	(0, 25)	(4, 12)	(0, 25)	(0, 25)	(4, 12)	(0, 25)
Acquisition mechanism	Parenteral	1 (4.55%)	0 (0.00%)	1 (4.17%)	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Sexual	2 (9.09%)	0 (0.00%)	2 (8.33%)	2 (7.41%)	0 (0.00%)	2 (6.67%)
	Vertical	3 (13.64%)	0 (0.00%)	3 (12.50%)	4 (14.81%)	0 (0.00%)	4 (13.33%)
	Unknown	16 (72.73%)	2 (100.00%)	18 (75.00%)	20 (74.07%)	3 (100.00%)	23 (76.67%)
Biopsy 1	Yes	12 (54.55%)	1 (50.00%)	13 (54.17%)	15 (55.56%)	2 (66.67%)	17 (56.67%)
	No	10 (45.45%)	1 (50.00%)	11 (45.83%)	12 (44.44%)	1 (33.33%)	13 (43.33%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Time from biopsy (years)	N	12	1	13	15	2	17
	Missing	0	0	0	0	0	0
	Mean (SD)	2.3 (4.0)	3.7 (.)	2.4 (3.9)	1.9 (3.7)	4.3 (0.8)	2.2 (3.5)
	95% CI	(-0.3. 4.8)	(.. .)	(0.0. 4.7)	(-0.1. 3.9)	(-3.2. 11.8)	(0.4. 4.0)
	Median	0.9	3.7	1.0	0.8	4.3	0.9
	(Q1, Q3)	(0.1. 1.8)	(3.7. 3.7)	(0.1. 2.2)	(0.1. 1.3)	(3.7. 4.9)	(0.1. 2.2)
	(Min, Max)	(0. 14)	(4. 4)	(0. 14)	(0. 14)	(4. 5)	(0. 14)
Inflamation Degree	1	1 (8.33%)	0 (0.00%)	1 (7.69%)	1 (6.67%)	0 (0.00%)	1 (5.88%)
	5	1 (8.33%)	0 (0.00%)	1 (7.69%)	1 (6.67%)	1 (50.00%)	2 (11.76%)
Fibrosis Stage Scale	Knodell	1 (8.33%)	0 (0.00%)	1 (7.69%)	1 (6.67%)	0 (0.00%)	1 (5.88%)
	Ishak	4 (33,33%)	1 (100,00%)	5 (38,46%)	5 (33,33%)	1 (50,00%)	6 (35,29%)
	Scheuer	2 (16,67%)	0 (0,00%)	2 (15,38%)	2 (13,33%)	0 (0,00%)	2 (11,76%)
	Metavir	5 (41,67%)	0 (0,00%)	5 (38,46%)	6 (40,00%)	1 (50,00%)	7 (41,18%)

		ITT Population HBV-DNA 24 weeks			Safety Population		
		Naïve	No Naïve	Total	Naïve	No Naïve	Total
Fibrosis stage unified grade	0	3 (25.00%)	0 (0.00%)	3 (23.08%)	3 (20.00%)	0 (0.00%)	3 (17.65%)
	1	6 (50.00%)	0 (0.00%)	6 (46.15%)	6 (40.00%)	0 (0.00%)	6 (35.29%)
	2	1 (8.33%)	1 (100.00%)	2 (15.38%)	2 (13.33%)	2 (100.00%)	4 (23.53%)
	3	2 (16.67%)	0 (0.00%)	2 (15.38%)	3 (20.00%)	0 (0.00%)	3 (17.65%)

Primary Efficacy Result(s)

HBV-DNA change visit 9 - visit 2 - ITT I poblation/PP population

		HBV-DNA 24 weeks					
		ITT population			Per protocol PP		
		Naïve	No Naïve	Total	Naïve	No Naïve	Total
HBV-DNA change (log 10 copies/ml) visit 9 - visit 2	N	22	2	24	13	1	14
	NMiss	0	0	0	0	0	0
	Mean (SD)	-5,4 (1,3)	-3,8 (0,5)	-5,3 (1,4)	-5,3 (1,5)	-4,2 (.)	-5,3 (1,5)
	95% IC	(-6,0, -4,8)	(-8,2, 0,6)	(-5,9, -4,7)	(-6,2, -4,4)	(., .)	(-6,1, -4,4)
	Median	-5,6	-3,8	-5,4	-5,6	-4,2	-5,6
	(Q1,Q3)	(-6,4, -4,9)	(-4,2, -3,5)	(-6,3, -4,4)	(-6,2, -4,6)	(-4,2, -4,2)	(-6,2, -4,2)
	(Min,Max)	(-8, -3)	(-4, -3)	(-8, -3)	(-8, -3)	(-4, -4)	(-8, -3)

Wilcoxon signed Rank sum text for the variation of HBV-DNA visit 9 - visit 2 – PP population -ITT I population

Population	Patients	N	Mean	SD	Statistic	p_value
Per protocol PP	Naïve	13	-5.35	1.49	-45.5	0.0002
ITT population HBV-DNA 24 weeks	Naïve	22	-5.45	1.35	-126.5	0.0000

Secondary efficacy Result (s)

The viral dynamics determination in the first four weeks was done in a subgroup a patients that finally involved only three patients of G. A.

HBV-DNA change from visit 9 to visit 2 according to the viral genotype –ITT Population.

		DNA-HBV population ITT 24 weeks				
		A	**D**	**E**	**F**	**Total**
HBV-DNA change (log 10 copias/ml) v9 - v2	N	8	12	1	3	24
	NMiss	0	0	0	0	0
	Mean (SD)	-5.9 (1.6)	-5.1 (1.1)	-6.5 (.)	-4.4 (1.4)	-5.3 (1.4)
	IC 95% MEAN	(-7.2. -4.5)	(-5.8. -4.4)	(.. .)	(-8.0. -0.9)	(-5.9. -4.7)
	Median	-5.8	-5.1	-6.5	-4.9	-5.4
	(Q1.Q3)	(-7.4. -4.6)	(-5.9. -4.3)	(-6.5. -6.5)	(-5.6. -2.8)	(-6.3. -4.4)
	(Min.Max)	(-8. -3)	(-7. -3)	(-7. -7)	(-6. -3)	(-8. -3)

Non-detectable HBV-DNA (< 300 copies/ml or 2,477 log10 copies/ml) per visit -ITT I Population.

		DNA-HBV population ITT 24 weeks		
		Naïve	**No Naïve**	**Total**
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v2	Yes	22 (100.00%)	2 (100.00%)	24 (100.00%)
	No	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v3	Yes	15 (68.18%)	1 (50.00%)	16 (66.67%)
	No	6 (27.27%)	1 (50.00%)	7 (29.17%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v4	Yes	16 (72.73%)	1 (50.00%)	17 (70.83%)
	No	6 (27.27%)	1 (50.00%)	7 (29.17%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v5	Yes	13 (59.09%)	0 (0.00%)	13 (54.17%)
	No	9 (40.91%)	2 (100.00%)	11 (45.83%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v6	Yes	8 (36.36%)	0 (0.00%)	8 (33.33%)

	No	14 (63.64%)	2 (100.00%)	16 (66.67%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v7	Yes	6 (27.27%)	0 (0.00%)	6 (25.00%)
	No	16 (72.73%)	2 (100.00%)	18 (75.00%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v8	Yes	4 (18.18%)	0 (0.00%)	4 (16.67%)
	No	17 (77.27%)	1 (100.00%)	18 (75.00%)
	Not available	1 (4.55%)	0 (0.00%)	1 (4.17%)
Non-detectable HBV-DNA (or < 2.477 log 10 copies/ml) v9	Yes	4 (18.18%)	0 (0.00%)	4 (16.67%)
	No	18 (81.82%)	2 (100.00%)	20 (83.33%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)

Percentage of patients with normalized ALT(ALT≤40 Units/L) per visit - ITT I population-PP population.

		HBV-DNA ITT Population 24 weeks			Per protocol PP		
		Naïve	No Naïve	Total	Naïve	No Naïve	Total
ALT normalized (≤ 40 Units / L) v1	Normal	0 (0.00%)	2 (100.00%)	2 (8.33%)	0 (0.00%)	1 (100.00%)	1 (7.14%)
	Abnormal	22 (100.00%)	0 (0.00%)	22 (91.67%)	13 (100.00%)	0 (0.00%)	13 (92.86%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v2	Normal	2 (9.09%)	2 (100.00%)	4 (16.67%)	1 (7.69%)	1 (100.00%)	2 (14.29%)
	Abnormal	20 (90.91%)	0 (0.00%)	20 (83.33%)	12 (92.31%)	0 (0.00%)	12 (85.71%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v3	Normal	3 (13.64%)	1 (50.00%)	4 (16.67%)	1 (7.69%)	1 (100.00%)	2 (14.29%)
	Abnormal	19 (86.36%)	0 (0.00%)	19 (79.17%)	12 (92.31%)	0 (0.00%)	12 (85.71%)
	Not available	0 (0.00%)	1 (50.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v4	Normal	5 (22.73%)	1 (50.00%)	6 (25.00%)	2 (15.38%)	1 (100.00%)	3 (21.43%)
	Abnormal	17 (77.27%)	1 (50.00%)	18 (75.00%)	11 (84.62%)	0 (0.00%)	11 (78.57%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

ALT normalized (≤ 40 Units / L) v5	Normal	10 (45.45%)	2 (100.00%)	12 (50.00%)	6 (46.15%)	1 (100.00%)	7 (50.00%)
	Abnormal	12 (54.55%)	0 (0.00%)	12 (50.00%)	7 (53.85%)	0 (0.00%)	7 (50.00%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v6	Normal	13 (59.09%)	2 (100.00%)	15 (62.50%)	7 (53.85%)	1 (100.00%)	8 (57.14%)
	Abnormal	9 (40.91%)	0 (0.00%)	9 (37.50%)	6 (46.15%)	0 (0.00%)	6 (42.86%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v7	Normal	12 (54.55%)	2 (100.00%)	14 (58.33%)	7 (53.85%)	1 (100.00%)	8 (57.14%)
	Abnormal	10 (45.45%)	0 (0.00%)	10 (41.67%)	6 (46.15%)	0 (0.00%)	6 (42.86%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v8	Normal	13 (59.09%)	1 (50.00%)	14 (58.33%)	7 (53.85%)	1 (100.00%)	8 (57.14%)
	Abnormal	8 (36.36%)	1 (50.00%)	9 (37.50%)	6 (46.15%)	0 (0.00%)	6 (42.86%)
	Not available	1 (4.55%)	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
ALT normalized (≤ 40 Units / L) v9	Normal	12 (54.55%)	2 (100.00%)	14 (58.33%)	8 (61.54%)	1 (100.00%)	9 (64.29%)
	Abnormal	10 (45.45%)	0 (0.00%)	10 (41.67%)	5 (38.46%)	0 (0.00%)	5 (35.71%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

ALT values in visit 2 and visit 9 – Security population.

		Security population		
		Naïve	**No Naïve**	**Total**
SGPT (ALT) (Units/L) visit 2	N	27	3	30
	Missing	0	0	0
	Mean (SD)	128.5 (162.1)	39.0 (11.5)	119.6 (155.9)
	95% IC	(64.4. 192.6)	(10.4. 67.6)	(61.4. 177.8)
	Median	65.0	40.0	59.0
	(Q1, Q3)	(46.0, 129.0)	(27.0, 50.0)	(44.0, 117.0)
	(Min, Max)	(22, 632)	(27, 50)	(22, 632)
SGPT (ALT) (Units/L) visit 9	N	24	2	26
	Missing	3	1	4
	Mean (SD)	41.3 (18.7)	29.0 (9.9)	40.3 (18.4)

	95% IC	(33.4, 49.2)	(-59.9, 117.9)	(32.9, 47.8)
	Median	37.5	29.0	36.5
	(Q1, Q3)	(26.0, 52.0)	(22.0, 36.0)	(25.0, 51.0)
	(Min, Max)	(15, 95)	(22, 36)	(15, 95)

Treatment adherence according to Morisky-Green and pill count. ITT I population.

		HBV-DNA 24 weeks. ITT population		
		Naïve	**No Naïve**	**Total**
Morisky-Green adherence	Compliant	20 (90.91%)	2 (100.00%)	22 (91.67%)
	Non-compliant	2 (9.09%)	0 (0.00%)	2 (8.33%)
Compliant patient with treatment (>=80%)	Yes	22 (100.00%)	2 (100.00%)	24 (100.00%)
	No	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Not available	0 (0.00%)	0 (0.00%)	0 (0.00%)

Safety Results (Safety population)

Adverse events summary. Security population.

		Security population		
		Naïve	**No Naïve**	**Total**
AE Yes/No	Yes	13 (48.15%)	2 (66.67%)	15 (50.00%)
	No	14 (51.85%)	1 (33.33%)	15 (50.00%)
Serious AE (Yes/No)	Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)
	No	13 (48.15%)	2 (66.67%)	15 (50.00%)
Severity	Mild	12 (44.44%)	2 (66.67%)	14 (46.67%)
	Moderate	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)
Related	Unsuspected	11 (40.74%)	1 (33.33%)	12 (40.00%)
	Suspected	2 (7.41%)	1 (33.33%)	3 (10.00%)
Continues?	Yes	7 (25.93%)	1 (33.33%)	8 (26.67%)
	No	6 (22.22%)	1 (33.33%)	7 (23.33%)

Note: 15 of 30 patients included in the in the security population have AEs

Adverse events by Preferred Term and System Organ Class. Security population.

		Security population		
		Naïve	**No Naïve**	**Total**
Additional exploration		1 (3.70%)	0 (0.00%)	1 (3.33%)
	Elevated blood creatinine	1 (3.70%)	0 (0.00%)	1 (3.33%)
Infections and infestations		3 (11.11%)	0 (0.00%)	3 (10.00%)
	Respiratory tract infection	2 (7.41%)	0 (0.00%)	2 (6.67%)
	Tooth infection	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Influenza	1 (3.70%)	0 (0.00%)	1 (3.33%)
Neoplasms benign, malignant and unspecified (included cysts and polyps)		1 (3.70%)	0 (0.00%)	1 (3.33%)
	Melanocytic nevus	1 (3.70%)	0 (0.00%)	1 (3.33%)
Skin and subcutaneous tissue disorders		1 (3.70%)	0 (0.00%)	1 (3.33%)
	Skin hyperpigmentation	1 (3.70%)	0 (0.00%)	1 (3.33%)
Nervous system disorders		1 (3.70%)	0 (0.00%)	1 (3.33%)
	Headache	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Sciatica	1 (3.70%)	0 (0.00%)	1 (3.33%)
Gastrointestinal disorders		6 (22.22%)	0 (0.00%)	6 (20.00%)
	Diarrhea	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Dyspepsia	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Dental pain	1 (3.70%)	0 (0.00%)	1 (3.33%)
	Gingivitis	1 (3,70%)	0 (0,00%)	1 (3,33%)
	Sickness	1 (3,70%)	0 (0,00%)	1 (3,33%)
	Esophageal varicose veins	1 (3,70%)	0 (0,00%)	1 (3,33%)
General disorders and alterations in the administration site		4 (14,81%)	1 (33,33%)	5 (16,67%)
	Asthenia	2 (7,41%)	1 (33,33%)	3 (10,00%)
	Influenza-like illness	1 (3,70%)	0 (0,00%)	1 (3,33%)
	Pyrexia	1 (3,70%)	0 (0,00%)	1 (3,33%)
Hepatobiliary disorders		1 (3,70%)	0 (0,00%)	1 (3,33%)
	Hypertransaminasemia	1 (3,70%)	0 (0,00%)	1 (3,33%)
Musculoskeletal and connective tissue disorders		4 (14,81%)	1 (33,33%)	5 (16,67%)

	Arthralgia	0 (0,00%)	1 (33,33%)	1 (3,33%)
	Backache	1 (3,70%)	0 (0,00%)	1 (3,33%)
	Myalgia	2 (7,41%)	0 (0,00%)	2 (6,67%)
	Toxic myopathy	1 (3,70%)	0 (0,00%)	1 (3,33%)
	Tendonitis	1 (3,70%)	0 (0,00%)	1 (3,33%)
Psychiatric disorders		1 (3,70%)	0 (0,00%)	1 (3,33%)
	Anxiety	1 (3,70%)	0 (0,00%)	1 (3,33%)
Respiratory, thoracic and mediastinal disorders		1 (3,70%)	0 (0,00%)	1 (3,33%)
	Sleep apnea syndrome	1 (3,70%)	0 (0,00%)	1 (3,33%)

Other Relevant Findings:

N.A.

Date of Clinical Trial Report

April 12 2010

Date Inclusion on Novartis Clinical Trial Results Database:

December 17, 2010

Date of Latest Update:

July 30 2010