



## Clinical trial results:

### An Open-label, Single-arm, Multicenter, Phase IV, 52-week Study to Evaluate the Efficacy and Safety of Telbivudine 600mg Tablets in Chinese Patients with Chronic Hepatitis B

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2016-001444-20    |
| Trial protocol           | Outside EU/EEA    |
| Global end of trial date | 16 September 2010 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 04 January 2017 |
| First version publication date | 04 January 2017 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLDT600ACN03 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00781105 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH 4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, +41 61324111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, +41 61324111, |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 16 September 2010 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 16 September 2010 |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

Main objective of the trial:

The main objective of the study was to evaluate the antiviral efficacy of telbivudine in terms of percentage of subjects achieving Hepatitis B virus (HBV) DNA <300 copies/millilitres (mL) at week 52.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 01 August 2008 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | China: 2211 |
| Worldwide total number of subjects   | 2211        |
| EEA total number of subjects         | 0           |

Notes:

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**Subjects enrolled per age group**

|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 26   |
| Adults (18-64 years)                      | 2183 |
| From 65 to 84 years                       | 2    |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 48 centers in China.

### Pre-assignment

Screening details:

A total of 2211 subjects were enrolled in the study.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Period (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Not applicable                  |
| Blinding used                | Not blinded                     |

Blinding implementation details:

The study was open label study, hence no blinding was performed

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes                                      |
| <b>Arm title</b>             | Hepatitis B 'e' antigen (HBeAg) positive |

Arm description:

Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Telbivudine        |
| Investigational medicinal product code |                    |
| Other name                             | Sebivo             |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects were orally administered with telbivudine 600 mg film coated tablets daily for a duration of 52 weeks.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Hepatitis B 'e' antigen (HBeAg) negative |
|------------------|--|

Arm description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Telbivudine        |
| Investigational medicinal product code |                    |
| Other name                             | Sebivo             |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects were orally administered with telbivudine 600 mg film coated tablets daily for a duration of 52 weeks.

| <b>Number of subjects in period<br/>1<sup>[1]</sup></b> | Hepatitis B 'e'<br>antigen (HBeAg)<br>positive | Hepatitis B 'e'<br>antigen (HBeAg)<br>negative |
|---|--|--|
| Started   | 1752   | 406  |
| Completed   | 1752   | 406  |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The ITT population, 97.6% (2158 patients) received at least one dose of Telbivudine and had at least one post-baseline assessment of serum HBV DNA (ITT population).

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Hepatitis B 'e' antigen (HBeAg) positive |
|-----------------------|--|

Reporting group description:

Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

|                       |  |
|-----------------------|--|
| Reporting group title | Hepatitis B 'e' antigen (HBeAg) negative |
|-----------------------|--|

Reporting group description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

| Reporting group values    | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative | Total |
|---------------------------|--|--|-------|
| Number of subjects        | 1752                                     | 406                                      | 2158  |
| Age categorical           |  |  |       |
| Units: Subjects           |  |  |       |
| Adolescents (12-17 years) | 25                                       | 1  | 26    |
| Adults (18-64 years)      | 1726                                     | 404                                      | 2130  |
| From 65-84 years          | 1  | 1  | 2     |
| Age continuous            |  |  |       |
| Units: years              |  |  |       |
| arithmetic mean           | 30.2                                     | 38.2                                     |       |
| standard deviation        | ± 9                                      | ± 10.49                                  | -     |
| Gender categorical        |  |  |       |
| Units: Subjects           |  |  |       |
| Female                    | 457                                      | 75                                       | 532   |
| Male                      | 1295                                     | 331                                      | 1626  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Hepatitis B 'e' antigen (HBeAg) positive |
| Reporting group description:<br>Subjects who were HBeAg positive with chronic hepatitis B (CHB) were orally administered with telbivudine 600 milligrams (mg) tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions. |  |
| Reporting group title   | Hepatitis B 'e' antigen (HBeAg) negative |
| Reporting group description:<br>Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.                                    |  |
| Subject analysis set title  | Safety population                        |
| Subject analysis set type   | Safety analysis                          |
| Subject analysis set description:<br>All subjects who received at least one dose of telbivudine 600 mg/day tablets and had at least one evaluable post-baseline safety assessment.  |  |

### Primary: Percentage of subjects achieving HBV DNA <300 copies/mL at Week 52

|  |   |
|--|---|
| End point title  | Percentage of subjects achieving HBV DNA <300 copies/mL at Week 52 <sup>[1]</sup> |
| End point description:<br>Undetectable serum HBV DNA was defined as HBV DNA <300 copies/mL determined by COBAS Taqman HBV assay. The assay utilized polymerase chain reaction (PCR) methods and automated sample readout technologies. The analysis was performed on Intent-to-treat (ITT) population defined as all subjects who received at least one dose of telbivudine 600 mg tablets and had at least one post-baseline assessment of serum HBV DNA. |   |
| End point type   | Primary   |
| End point timeframe:<br>From Baseline to Week 52   |   |
| Notes:   |   |

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

| End point values                 | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed      | 1749                                     | 405                                      |  |  |
| Units: Percentage                |  |  |  |  |
| number (confidence interval 95%) | 54.3 (51.79 to 56.74)                    | 86.5 (82.5 to 89.82)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of subjects achieving HBV DNA <300 copies/mL at Week 24

|                 |  |
|-----------------|--|
| End point title | Percentage of subjects achieving HBV DNA <300 copies/mL at Week 24 |
|-----------------|--|

End point description:

Undetectable serum HBV DNA was defined as HBV DNA <300 copies/mL determined by COBAS Taqman HBV assay. The assay utilized PCR methods and automated sample readout technologies. The analysis was performed on ITT population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 24

| End point values                 | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed      | 1749                                     | 405                                      |  |  |
| Units: Percentage                |  |  |  |  |
| number (confidence interval 95%) | 36.2 (33.92 to 38.53)                    | 82.6 (78.47 to 86.18)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean reduction in HBV DNA from baseline at Week 12, 24, 36 and 52

|                 |   |
|-----------------|---|
| End point title | Mean reduction in HBV DNA from baseline at Week 12, 24, 36 and 52 |
|-----------------|---|

End point description:

HBeAg loss was defined as serum HBeAg undetectable in a subject and HBeAg seroconversion was defined as serum HBeAg undetectable and anti-HBe detectable with HBeAg detectable at baseline. In HBeAg positive subjects, loss of detectable serum HBsAg (HBeAg loss) with gain of detectable anti-HBe antibody (HBeAg seroconversion), usually indicated a subject's transition to a state of substantially lower HBV replication. HBV serologic markers were assessed using standard commercially-available assays. This analysis was performed on ITT population for only those subjects who were HBeAg positive at baseline. The analysis was done using a last observation carried forward approach.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Baseline, Week 12, Week 24, Week 36 and Week 52

| End point values                     | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed          | 1749                                     | 405                                      |  |  |
| Units: Log <sup>10</sup> copies/ mL  |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 12 (n = 1726, 400)              | -4.17 (± 1.25)                           | -3.57 (± 1.344)                          |  |  |
| Week 24 (n = 1741, 402)              | -4.91 (± 1.449)                          | -4.2 (± 1.351)                           |  |  |

|                         |                 |                 |  |  |
|-------------------------|-----------------|-----------------|--|--|
| Week 36 (n = 1742, 402) | -5.13 (± 1.605) | -4.27 (± 1.477) |  |  |
| Week 52 (n = 1744, 402) | -5.07 (± 1.917) | -4.2 (± 1.663)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of HBeAg positive subjects with HBeAg loss and seroconversion at Week 52

|                 |  |
|-----------------|--|
| End point title | Percentage of HBeAg positive subjects with HBeAg loss and seroconversion at Week 52 <sup>[2]</sup> |
|-----------------|--|

End point description:

HBeAg loss was defined as serum HBeAg undetectable in a subject with HBeAg detectable at baseline. HBeAg seroconversion was defined as serum HBeAg undetectable and anti-HBe detectable in subjects with HBeAg detectable at baseline. In HBeAg positive subjects, loss of detectable serum HBsAg (HBeAg loss) with gain of detectable anti-HBe antibody (HBeAg seroconversion), usually indicated a subject's transition to a state of substantially lower HBV replication. HBV serologic markers were assessed using standard commercially-available assays at week 52 from baseline. This analysis was performed on ITT population for only those subjects who were HBeAg positive at baseline. The analysis was done using a last observation carried forward approach.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 52

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Percentage of subjects with HBeAg loss/ seroconversion at week 52 was evaluated only for those subjects who were HBeAg positive at baseline.

| End point values                 | Hepatitis B 'e' antigen (HBeAg) positive |  |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                          |  |  |  |
| Number of subjects analysed      | 1752                                     |  |  |  |
| Units: Percentage                |  |  |  |  |
| number (confidence interval 95%) |  |  |  |  |
| HBeAg loss                       | 22.7 (20.78 to 24.76)                    |  |  |  |
| HBeAg seroconversion             | 19.6 (17.74 to 21.52)                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with Alanine aminotransferase (ALT) normalization at Week 24 and Week 52

|                 |   |
|-----------------|---|
| End point title | Percentage of subjects with Alanine aminotransferase (ALT) normalization at Week 24 and Week 52 |
|-----------------|---|



End point description:

ALT normalization was defined as ALT level returning to below upper limit of normal (ULN). ALT levels were determined from serum samples at study site using standard methods. The analysis was performed on ITT population. The analysis was done using a last observation carried forward approach.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Baseline, Week 24 and Week 52

| End point values                 | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed      | 1670                                     | 356                                      |  |  |
| Units: Percentage                |  |  |  |  |
| number (confidence interval 95%) |  |  |  |  |
| Week 24 (n = 1670, 356)          | 73.8 (71.64 to 75.93)                    | 78.2 (73.58 to 82.44)                    |  |  |
| Week 52 (n = 1670, 356)          | 81.3 (79.35 to 83.16)                    | 78 (73.28 to 82.18)                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with HBsAg loss and seroconversion at Week 52

|                 |  |
|-----------------|--|
| End point title | Percentage of subjects with HBsAg loss and seroconversion at Week 52 |
|-----------------|--|

End point description:

Hepatitis B surface antigen (HBsAg) loss was defined as serum HBsAg undetectable in a subject with HBsAg detectable at baseline. HBsAg seroconversion was defined as serum HBsAg undetectable and HB surface antibody (anti-HBs) detectable in a patient with HBsAg detectable at baseline. Serum HBsAg and seroconversion was assessed using standard commercially-available enzyme immunoassays. This analysis was performed on ITT population. The analysis was done using a last observation carried forward approach.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 52

| End point values                 | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed      | 1752                                     | 406                                      |  |  |
| Units: Percentage                |  |  |  |  |
| number (confidence interval 95%) |  |  |  |  |

|                      |                    |                    |  |  |
|----------------------|--------------------|--------------------|--|--|
| HBsAg loss           | 0.5 (0.2 to 0.9)   | 0.2 (0.01 to 1.37) |  |  |
| HBsAg seroconversion | 0.2 (0.06 to 0.59) | 0.2 (0.01 to 1.37) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of subjects with virologic breakthrough at Week 52

|                 |   |
|-----------------|---|
| End point title | Percentage of subjects with virologic breakthrough at Week 52 |
|-----------------|---|

End point description:

Virologic breakthrough was defined as HBV DNA  $\geq 1$  log 10 copies/mL from nadir on two consecutive visits or at last on-treatment visit for subjects on treatment who achieved HBV DNA  $\geq 1$  log 10 copies/mL (10-fold) reduction from baseline on two consecutive visits. Subjects who had not achieved a reduction from baseline in HBV DNA but did exhibit an increase  $\geq 1$  log 10 were not indicative of virologic breakthrough but could be a result of primary non-response instead. This analysis was performed on ITT population and included patients who were under treatment at the week 52 visit and who were not previously treated with immune modulators or nucleos(t)ides. The analysis was done using a last observation carried forward approach.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 52

| End point values            | Hepatitis B 'e' antigen (HBeAg) positive | Hepatitis B 'e' antigen (HBeAg) negative |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                          | Reporting group                          |  |  |
| Number of subjects analysed | 1752                                     | 406                                      |  |  |
| Units: Percentage           |  |  |  |  |
| number (not applicable)     | 6.8                                      | 5.2                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs and drug related AEs leading to discontinuation, study medication interruption (not discontinuation due to AE) and who died

|                 |  |
|-----------------|--|
| End point title | Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs and drug related AEs leading to discontinuation, study medication interruption (not discontinuation due to AE) and who died |
|-----------------|--|

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other

conditions which in judgment of investigators represent significant hazards. Adverse events of special interest (AESI) depended on severity and relationship to telbivudine. The analysis was done on safety population.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From Baseline to 30 days after last dose of study treatment |           |

| End point values                            | Safety population    |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                          | Subject analysis set |  |  |  |
| Number of subjects analysed                 | 2206                 |  |  |  |
| Units: Subjects                             |                      |  |  |  |
| AEs   | 246                  |  |  |  |
| AESIs                                       | 131                  |  |  |  |
| SAEs  | 28                   |  |  |  |
| AEs leading to discontinuation              | 27                   |  |  |  |
| Drug related AEs leading to discontinuation | 24                   |  |  |  |
| Study medication interruption               | 6                    |  |  |  |
| Death                                       | 1                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with Grade 3 or 4 laboratory abnormalities

|  |   |
|--|---|
| End point title  | Number of subjects with Grade 3 or 4 laboratory abnormalities |
| End point description:   |   |
| Laboratory abnormalities were analyzed by shift tables and each subject was counted only once. New onset grade 3/4 abnormalities of the laboratory parameters from baseline to week 52 were analyzed for hematology, serum biochemistry and urinalysis. "New onset" was defined as laboratory assessments with increased toxicity grades compared with baseline values. Limits for GRADE 3 lab abnormalities were: Hematology; absolute neutrophil count (500-749 /millimeter cube (mm <sup>3</sup> )), hemoglobin (6.4 - < 8 grams (g)/ deciliter (dl)), platelet count (20,000-49,999/mm <sup>3</sup> ), prothrombin time (1.5-3.0 ULN), White Blood Cell (1.0 - <5.0*10 <sup>9</sup> / Litres (L)); Clinical Biochemistry; ALT (3- 10*baseline) ,AST (3- 10*baseline), albumin (2.0-2.5 g/L), amylase (>3 - 10*ULN), creatine kinase (>7 - 10*ULN), creatinine (>3 - 6.0*ULN), total bilirubin (>5 -10*ULN) and urinalysis( protein: 2- 3.5 g loss per day OR > =1% OR > = 10 g/L). |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Baseline to Week 52   |   |

| End point values            | Safety population    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 2206                 |  |  |  |
| Units: Subjects             |                      |  |  |  |
| Absolute neutrophil Count   | 2                    |  |  |  |
| Hemoglobin                  | 1                    |  |  |  |
| Platelet count              | 12                   |  |  |  |
| Prothrombin Time            | 7                    |  |  |  |
| White Blood Cell            | 1                    |  |  |  |
| ALT                         | 25                   |  |  |  |
| AST                         | 19                   |  |  |  |
| Albumin                     | 0                    |  |  |  |
| Amylase                     | 0                    |  |  |  |
| Creatine Kinase             | 69                   |  |  |  |
| Creatinine                  | 0                    |  |  |  |
| Total bilirubin             | 0                    |  |  |  |
| Urinalysis (Protein)        | 2                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with clinically significant changes in vital signs

|                 |   |
|-----------------|---|
| End point title | Number of subjects with clinically significant changes in vital signs |
|-----------------|---|

End point description:

Subjects with vital signs namely blood pressure (BP): systolic blood pressure (SBP) millimeter of mercury (mmHg): result <90, result >180, or change > 20; diastolic BP (DBP) (mmHg): result <50, result >105, or change>15; heart rate (bpm): result<50, result >120, or change > 15 outside the defined normal range were graded as clinically significant vital signs. The analysis was performed on the safety population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 52

| End point values            | Safety population    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 2206                 |  |  |  |
| Units: Subjects             |                      |  |  |  |
| Low SBP                     | 1                    |  |  |  |
| High DBP                    | 1                    |  |  |  |
| Low heart rate              | 1                    |  |  |  |
| High heart rate             | 1                    |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Adverse event reporting additional description:

AE additional description

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | HBeAg negative |
|-----------------------|----------------|

Reporting group description:

Subjects who were HBeAg negative with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions.

|                       |                |
|-----------------------|----------------|
| Reporting group title | HBeAg positive |
|-----------------------|----------------|

Reporting group description:

Subjects who were HBeAg positive with CHB were orally administered with telbivudine 600 mg tablets daily for a duration of 52 weeks. Dose modification was done for subjects who were unable to tolerate the treatment and had moderate to severe adverse reactions

| Serious adverse events  | HBeAg negative  | HBeAg positive    |  |
|---|-----------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                 |                   |  |
| subjects affected / exposed   | 5 / 420 (1.19%) | 23 / 1786 (1.29%) |  |
| number of deaths (all causes)                                       | 0               | 1                 |  |
| number of deaths resulting from adverse events                      | 0               | 0                 |  |
| Investigations  |                 |                   |  |
| Blood creatine phosphokinase increased                              |                 |                   |  |
| subjects affected / exposed   | 1 / 420 (0.24%) | 5 / 1786 (0.28%)  |  |
| occurrences causally related to treatment / all                     | 1 / 1           | 4 / 5             |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0             |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                   |  |
| Hepatic neoplasm malignant  |                 |                   |  |
| subjects affected / exposed   | 0 / 420 (0.00%) | 1 / 1786 (0.06%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 1             |  |
| Rectal cancer   |                 |                   |  |

|  |                 |                  |  |
|--|-----------------|------------------|--|
| subjects affected / exposed                          | 1 / 420 (0.24%) | 0 / 1786 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Teratoma   |                 |                  |  |
| subjects affected / exposed                          | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Injury, poisoning and procedural complications       |                 |                  |  |
| Femoral neck fracture                                |                 |                  |  |
| subjects affected / exposed                          | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Congenital, familial and genetic disorders           |                 |                  |  |
| Heart block congenital                               |                 |                  |  |
| subjects affected / exposed                          | 1 / 420 (0.24%) | 0 / 1786 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Surgical and medical procedures                      |                 |                  |  |
| Internal fixation of fracture                        |                 |                  |  |
| subjects affected / exposed                          | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Nervous system disorders                             |                 |                  |  |
| Subarachnoid haemorrhage                             |                 |                  |  |
| subjects affected / exposed                          | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| General disorders and administration site conditions |                 |                  |  |
| Fatigue  |                 |                  |  |
| subjects affected / exposed                          | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Mucous membrane disorder                             |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal disorders                      |                 |                  |  |
| Reflux gastritis                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Reproductive system and breast disorders        |                 |                  |  |
| Ovarian cyst                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                 |                  |  |
| Muscular weakness                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 2 / 1786 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Musculoskeletal pain                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 420 (0.24%) | 0 / 1786 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myalgia   |                 |                  |  |
| subjects affected / exposed                     | 1 / 420 (0.24%) | 3 / 1786 (0.17%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 4 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myopathy  |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 5 / 1786 (0.28%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myositis  |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Infections and infestations</b>              |                 |                  |  |
| Appendicitis                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 2 / 1786 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatitis B                                     |                 |                  |  |
| subjects affected / exposed                     | 2 / 420 (0.48%) | 2 / 1786 (0.11%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nasopharyngitis                                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia                                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 420 (0.00%) | 1 / 1786 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | HBeAg negative   | HBeAg positive    |  |
|---|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                  |                   |  |
| subjects affected / exposed                           | 20 / 420 (4.76%) | 74 / 1786 (4.14%) |  |
| <b>Investigations</b>                                 |                  |                   |  |
| Blood creatine phosphokinase increased                |                  |                   |  |
| subjects affected / exposed                           | 20 / 420 (4.76%) | 74 / 1786 (4.14%) |  |
| occurrences (all)                                     | 20               | 79                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 11 March 2009 | <p>Part of the inclusion criteria had been changed as following:</p> <ul style="list-style-type: none"> <li>*Central lab detected serum HBV DNA level <math>\geq 10^5</math> copies/mL for HBeAg positive subjects; <math>\geq 10^4</math> copies/mL for HBeAg negative subjects at the screening visit</li> <li>*Elevated serum ALT <math>\geq 1.3 \times \text{ULN}</math> and <math>&lt; 10 \times \text{ULN}</math> at screening visit (non- HBV factors' impact on ALT was excluded, such as drug or alcohol).</li> </ul> <p>Part of the exclusion criteria had been changed as following:</p> <ul style="list-style-type: none"> <li>*Subject had a history of or clinical signs/symptoms of hepatic decompensation such as evidenced by ascites, esophageal variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis; or Child- Pugh Grade B or C.</li> <li>*Subject had any of the following laboratory values during screening period: <ul style="list-style-type: none"> <li>a. Hemoglobin <math>&lt; 11</math> g/dL for men or <math>&lt; 10</math> g/dL for women</li> <li>b. Total WBC <math>&lt; 3,500/\text{mm}^3</math></li> <li>c. Absolute neutrophil count (ANC) <math>&lt; 1,500/\text{mm}^3</math></li> <li>d. Platelet count <math>&lt; 80,000/\text{mm}^3</math></li> <li>e. Serum albumin <math>&lt; 3.5</math> g/dL</li> <li>f. Total bilirubin <math>\geq 2.0</math> mg/dL</li> <li>g. Serum creatinine <math>\geq 1.5</math> mg/dL</li> <li>h. Serum creatine kinase <math>\geq 5 \times \text{ULN}</math></li> <li>i. PT prolongation by <math>\geq 3</math> sec (based on the ULN of the reference value) or PTA <math>\leq 60\%</math></li> <li>j. Serum amylases <math>\geq 1.5 \times \text{ULN}</math>.</li> </ul> </li> </ul> <p>Following changes to Appendix 1 were made:</p> <ol style="list-style-type: none"> <li>1. All drugs other than protocol defined anti-HBV medications: lamivudine, adefovir, entecavir, tenofovir, emtricitabine (FTC), lobucavir, etc.</li> <li>2. Any type of immunomodulators: interferons (PEG-, or alpha-, beta-, gamma-interferon, etc.), thymosin, IL-12, or other recognized systemic immunomodulators</li> <li>3. Liver protectors and/or enzyme reducers, including but were not limited to (e.g. herbal medications, Diammonium glycyrrhizinate, shizandrin A, bifendate, sedum sarmentosum beg, potassium and magnesium aspartate, reduced glutathione, oxymatrine, etc.).</li> <li>4. Prolonged use of systemic acyclovir, famciclovir or ganciclovir defined as episodic treatment with these agents for periods exceeding 10 days every 3 months, or chronic suppressive therapy.</li> </ol> |
| 11 March 2009 | <p>Continued from above:</p> <ol style="list-style-type: none"> <li>5. Systemic corticosteroids (topical and inhaled corticosteroids were permitted).</li> <li>6. Hepatotoxic drugs (e.g., dapsone, erythromycin, fluconazole, ketoconazole, rifampin or anti-tuberculosis drugs, toxic doses of acetaminophen), as well as herbal medications known to cause hepatotoxicity (e.g., St. John's Wart, milk thistle, Kava, Jin Bu Huan, Yuzhitang, germander, chaparral, shark cartilage, mistletoe, slim 10, Lipokinetix, etc.).</li> <li>7. Nephrotoxic drugs (e.g., non-steroidal anti-inflammatory use, aminoglycosides, amphotericin B, foscarnet, etc.).</li> <li>8. Alcohol or illicit drug abuse. For the purposes of the present study, alcohol abuse was arbitrarily defined as frequent consumption of alcoholic beverages with an average daily intake of more than 40g of ethanol.</li> <li>9. Drugs associated with myopathy, including corticosteroids, chloroquine, hydroxychloroquine, certain HMGCoA reductase inhibitors, fibric acid derivatives, penicillamine, zidovudine, cyclosporine, erythromycin, niacin, and/or azole antifungals.</li> </ol>   |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported