

Byung Chul Yoo

Samsung Medical Center, Seoul, Korea

I have no financial relationship within the last 12 months relevant to my presentation.

AND

My presentation does include discussion of off-label or investigational use.

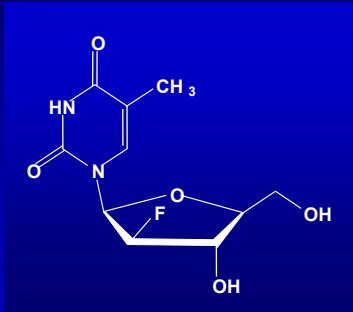
(Clevudine)

A 24-week Clevudine monotherapy produced profound on-treatment viral suppression as well as sustained viral suppression and normalization of aminotransferase levels for 24 weeks off-treatment in HBeAg(+) chronic hepatitis B patients.

B.C. Yoo¹, J.H. Kim², K.S. Lee³, T.H. Kim⁴, S.W. Paik¹, S.H. Ryu⁵, J.Y. Han⁶, M. Cho⁷, S.G. Hwang⁸, B.I. Kim⁹, Y.S. Lee⁶, H.C. Kim¹⁰, J.S. Hwang¹¹, S.K. Choi¹², Y.S. Kim¹³, Y.O. Kweon¹⁴, J.Y. Choi⁶, H.Y. Lee¹⁵, H.W. Yoo¹⁶, M.J. Otto¹⁷, P.A. Furman¹⁷, H.S. Lee¹⁸

¹Samsung Medical Center ²Gachon Medical School ³Yonsei University Hospital ⁴Ewha Womans University Hospital ⁵Inje University Seoul Paik Hospital ⁶The Catholic University of Korea ⁷Pusan National University Hospital ⁸Pochon CHA University Hospital ⁹Kangbuk Samsung Medical Center ¹⁰Wonkwang University Hospital ¹¹Keimyung University Dongsan Medical Center ¹²Chonnam National University Hospital ¹³Soon Chun Hyang University Hospital ¹⁴Kyungpook National University Hospital ¹⁵Chungnam National University Hospital ¹⁶Bukwang Pharm. Co., Ltd. ¹⁷Pharmasset Inc. ¹⁸Seoul National University Hospital

Clevudine (L-FMAU)



- Pyrimidine nucleoside analogue, L- enantiomer
- Potent inhibitor of hepatitis B virus *in vitro* ($EC_{50} = 0.02$ to $0.84 \mu\text{M}$)
- Demonstrated antiviral activity in duck and woodchuck models of chronic hepatitis B infection

L-FMAU, 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)thymine

Pharmacologic Characteristics

1. Potent inhibition of HBV and EBV replication
 - Inhibition of synthesis of ds-DNA from ss-DNA
 - Suppression of CCC-DNA
2. No interference on human DNA polymerases
3. No cytotoxicity or mitochondrial toxicity
4. Rapid absorption, high bioavailability, long half life
5. Major route of elimination: renal excretion

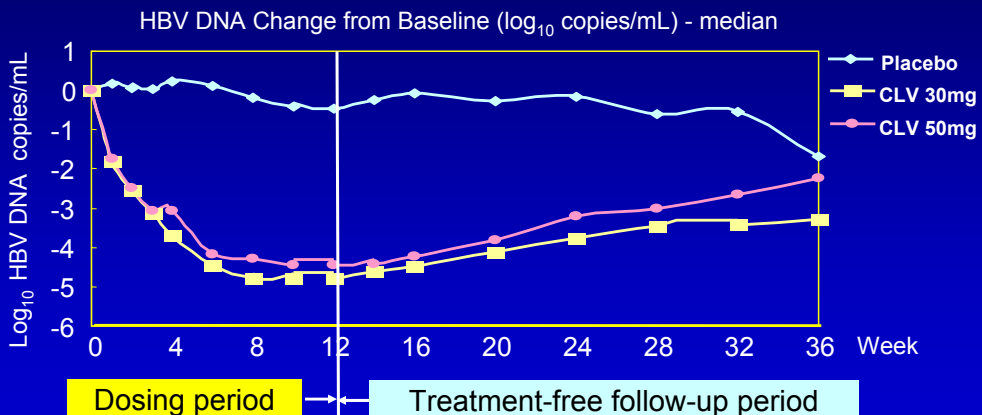
L-FMAU-201

A 12-Week Clevudine Therapy Showed Prolonged Antiviral Activities and Normalization of ALT Levels for 6-Months after Discontinuation of Treatment in Patients with Chronic Hepatitis B

H-S Lee, Y-H Chung, KS Lee, KS Byun, SW Paik, JY Han, K Yoo, JH Lee, SG Hwang and BC Yoo.

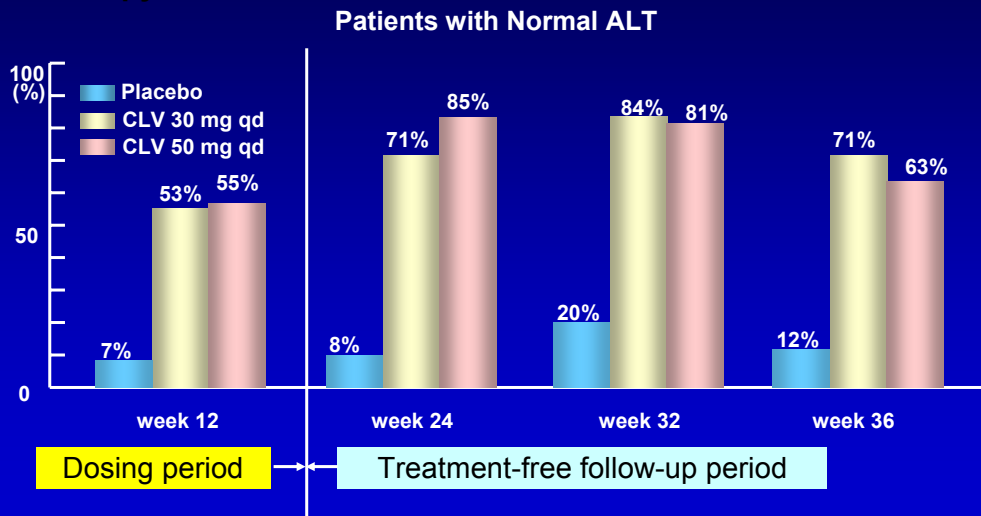
Hepatology 2004;40(S):652A

- Clevudine showed potent antiviral activities during therapy for 12 weeks.
- Clevudine characteristically induced sustained post-treatment antiviral effect after a 12-week treatment period.



Hepatology. 2004;40(S):652A

Majority of patients showed normalization of ALT at the end of a 12-week Clevudine therapy, which was maintained for at least 24-week off therapy.



L-FMAU-301 Study Design

- ◆ A double-blind, randomized, parallel, placebo-controlled study in HBeAg(+) CHB patients
- ◆ Treatment with clevudine 30mg QD or Placebo for 24 weeks
Clevudine 30 mg : Placebo = 3 : 1
- ◆ Follow-up for 24 weeks after cessation of dosing
- ◆ Multicenter study at 33 sites in Korea

Inclusion and Exclusion Criteria

Inclusion Criteria

- HBsAg positive for > 6 months
- HBeAg positive and anti-HBe negative
- HBV DNA $\geq 1 \times 10^6$ copies/mL
- $1.2 \leq$ ALT values $\leq 15 \times$ ULN at screening

Exclusion Criteria

- HIV- and HCV positive
- evidence of cirrhosis or hepatocellular carcinoma
- treatment with interferon within 6 months of screening
- previous treatment with any nucleoside analogue

Study Endpoints

➤ **Primary Endpoints**

Antiviral activity - median change in \log_{10} HBV DNA from baseline

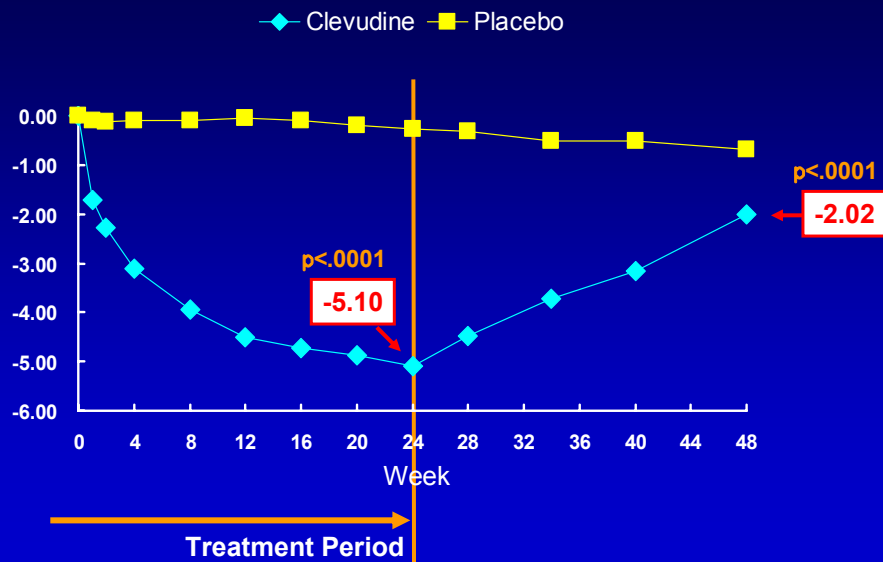
➤ **Secondary Endpoints**

- 1) Antiviral activity - proportion of patients with HBV DNA levels below LOD of the assays
Digene HC II assay : <4,700 copies/mL
Amplicor PCR assay : <300 copies/mL
- 2) Biochemical improvement – normal ALT
- 3) Serology - HBeAg loss and/or seroconversion

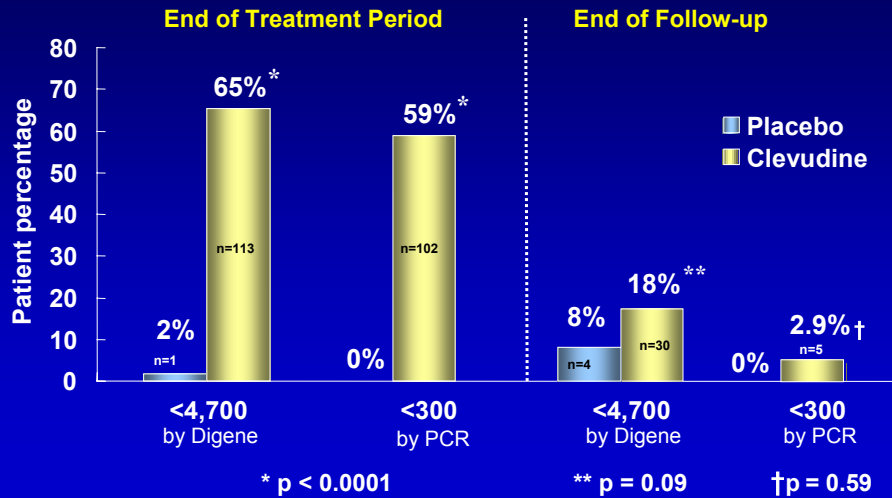
Subject Characteristics at Baseline

| | Clevudine 30mg (n=182) | Placebo (n=61) | p-value |
|--|---------------------------|-------------------|---------|
| Median Age (years) | 38 | 34 | 0.1214 |
| Gender (n, %) | | | |
| Male | 149 (82%) | 43 (70%) | 0.059 |
| Female | 33 (18%) | 18 (30%) | |
| Median Serum HBV DNA (log ₁₀ copies/mL) | 8.29 | 8.38 | 0.5021 |
| Median ALT (IU/L) | 124 | 128 | 0.1721 |
| Mean ALT (IU/L)(SE) | 159.7(8.5) | 186.8(23.0) | 0.1721 |
| Genotype C | 100% | 100% | |

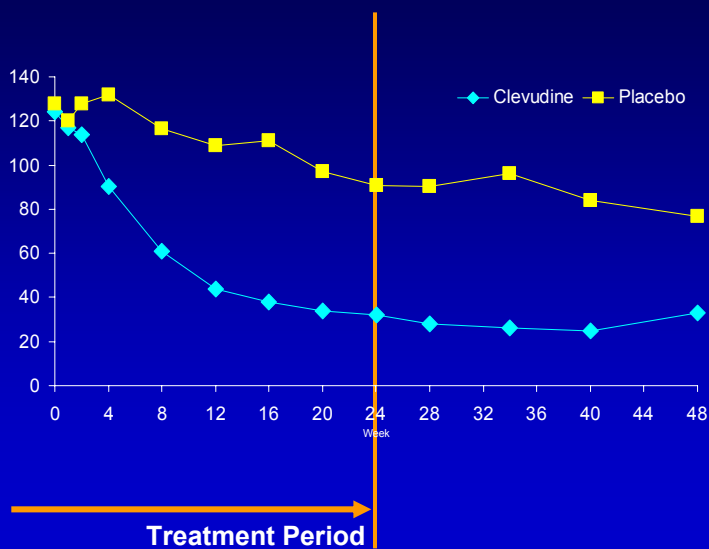
Viral Change (median) from Baseline (log₁₀ copies/mL)



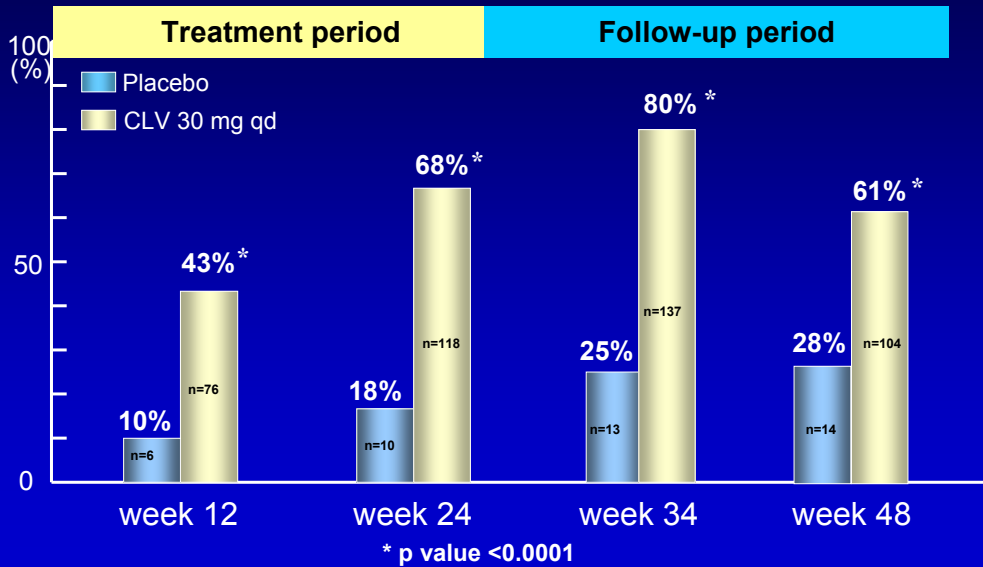
Study 301 Secondary Endpoints Proportion of Patients Achieving Undetectable HBV (copies/mL)



Median ALT Change over Time



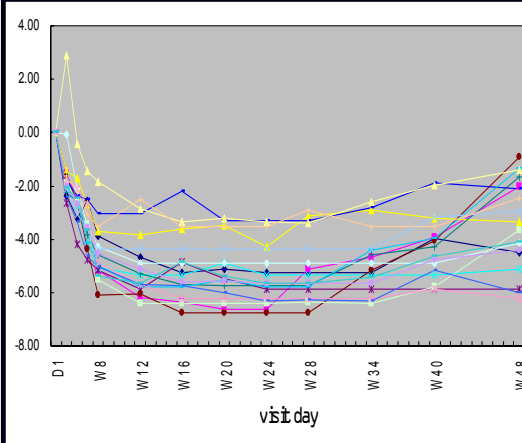
Secondary Endpoint Proportion of Patients with Normal ALT in Study 301



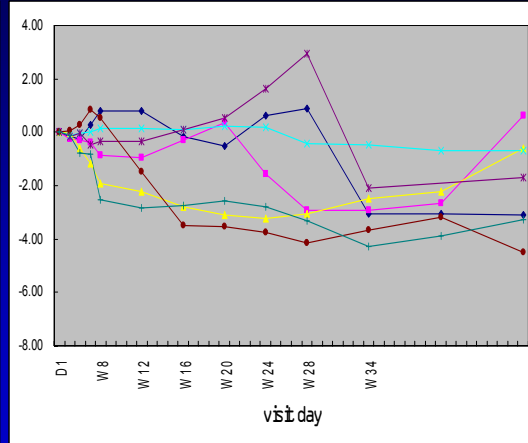
Secondary Endpoint Serologic Response

| | Clevudine | | Placebo | |
|-------------------------|------------------------|------------------------|------------------------|------------------------|
| | Week 24 (treatment) | Week 48 (follow-up) | Week 24 (treatment) | Week 48 (follow-up) |
| HBeAg loss | 18/173 (10.4%) | 26/170 (15.3%) | 7/57 (12.3%) | 6/50 (12%) |
| HBeAb conversion | 12/173 (6.9%) | 17/170 (10%) | 5/57 (8.8%) | 6/50 (12%) |

The log₁₀ change in HBV DNA in the patients with HBeAg loss at Week 24



Clevudine group (18 pts)



Placebo group (7 pts)

Incidence of Most Frequently Reported Adverse Events During the Treatment Period

| Adverse events ^a | Clevudine 30mg n=182 (%) | Placebo n=61 (%) |
|-----------------------------|-----------------------------|---------------------|
| INFECTION | 26 (14.3) | 10 (16.4) |
| ASTHENIA | 20 (11.0) | 6 (9.8) |
| ABDOMINAL PAIN | 11 (6.0) | 5 (8.2) |
| HEADACHE | 10 (5.5) | 3 (4.9) |
| DYSPEPSIA | 13 (7.1) | 4 (6.6) |
| DIARRHEA | 9 (5.0) | 4 (6.6) |
| ALT INCREASED | 5 (2.8) | 9 (14.8) |

^a This table includes all AEs occurring in more than 5% while on treatment. Each patient is counted only once per treatment period for each AE.

Incidence of \geq Grade 3 Laboratory Abnormality During the Treatment Period

| | Clevudine 30mg n=182 (%) | Placebo n=61 (%) | p-value |
|------------------------|-----------------------------|---------------------|---------|
| ALT | 35 (19.2%) | 22 (36.1%) | 0.0068 |
| AST | 14 (7.7%) | 13 (21.3%) | 0.0032 |
| Creatine phosphokinase | 6 (3.3%) | 3 (4.9%) | 0.6946 |
| GGT | 1 (0.6%) | 1 (1.6%) | 0.4383 |
| Glucose | 1 (0.6%) | 1 (1.6%) | 0.4383 |
| Lipase | 2 (1.1%) | 0 (0%) | 1 |
| Prothrombin time | 4 (2.2%) | 3 (4.9%) | 0.371 |

Note : This table includes all \geq Grade 3 Laboratory Abnormality occurring in more than 1 % while on treatment. If a new or worsening from baseline toxicity reported more than once for a test, the maximum grade is presented.

Genotypic Analysis

Nucleotide substitutions at 24 weeks

- clevudine group : rtA181A/T (n=5), rtV191V/I (n=1) in the 5 patients
- placebo group : rtL132M (n=1), rtA181S (n=1), rtV191V/I (n=2) in the 4 patients

Overall, none of the observed mutations was associated with a rebound in HBV DNA levels during the treatment period.

Summary

- Clevudine 30mg QD for 24 weeks was well tolerated and showed potent antiviral activity in HBeAg(+) CHB patients.
- Clevudine characteristically induced sustained viral suppression and normalization of ALT for 6 months after cessation of dosing
- No emergence of resistant mutants during therapy

Unique Antiviral Features of Clevudine

- ✓ Potent anti-HBV activity
- ✓ Excellent ALT normalization
- ✓ Sustained viral suppression off therapy
- ✓ No emergence of resistant mutants
- ✓ Excellent safety/tolerability profiles
- ✓ Suppression of cccDNA
- ✓ Suppression of viral antigens