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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.

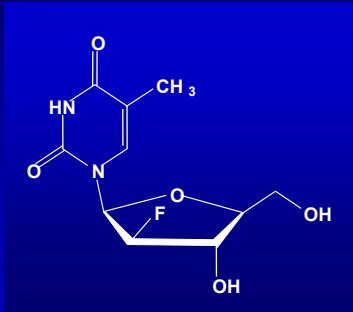
(Clevudine)

Clevudine is highly efficacious in HBeAg(-) chronic hepatitis B patients with a sustained antiviral effect after cessation of therapy

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Clevudine (L-FMAU)



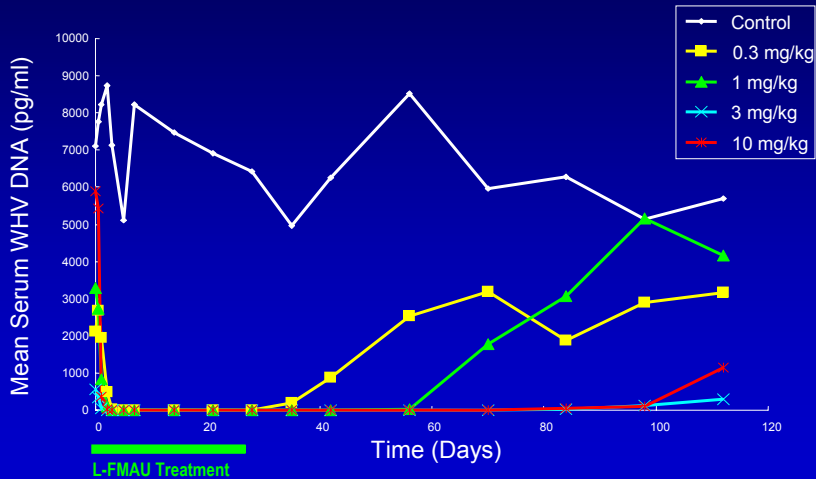
- Pyrimidine nucleoside analogue, L- enantiomer
- Potent inhibitor of hepatitis B virus *in vitro* ($EC_{50} = 0.02$ to $0.84 \mu\text{M}$)
- Demonstrated antiviral activity in duck and woodchuck models of chronic hepatitis B infection

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

Pharmacologic Characteristics

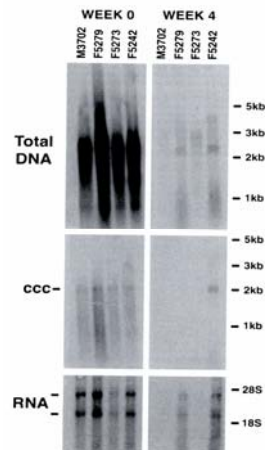
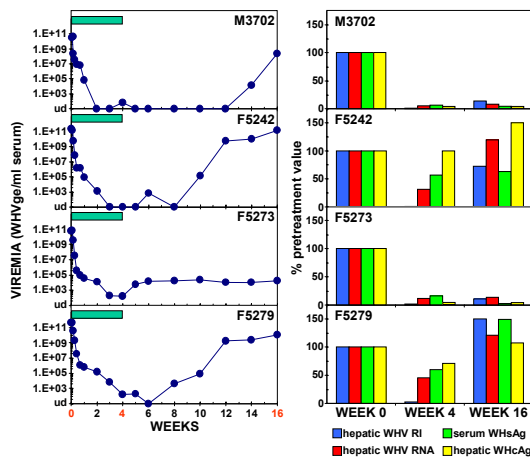
1. Potent inhibition of HBV and EBV replication
 - Inhibition of synthesis of ds-DNA from ss-DNA
 - Suppression of CCC-DNA
2. No interference on human DNA polymerases
3. No cytotoxicity or mitochondrial toxicity
4. Rapid absorption, high bioavailability, long half life
5. Major route of elimination: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

Mean Serum WHV DNA of Woodchucks Treated With Varying Doses of Clevudine for 28 days (n=4/group)*



* Peek SF et al. Hepatology. 2001;33:254-66

Retention of Antiviral Effects Following Withdrawal of Clevudine Treatment for 4 weeks is Correlated with Reduction of cccDNA



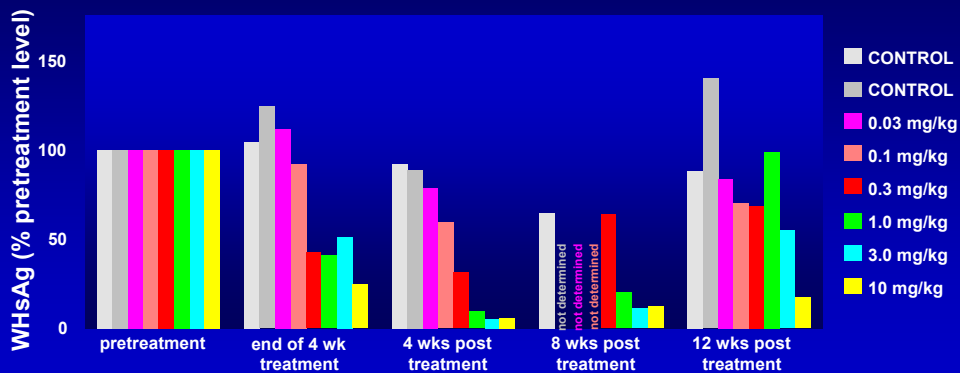
Peek SF et al. Hepatology. 2001;33:254-66

The loss of cccDNA during Clevudine Treatment

Animal	Weeks of therapy	cccDNA per hepatocyte	Cells assayed	Viral-cell joints detected	Viral -cell joints per cell
WC343	0	63	440	6	0.014
	6	8	380	5	0.013
	15	8	500	8	0.016
	30	0.8	420	12	0.029
WC345	0	41	206	10	0.049
	6	18	75	4	0.053
	15	19	270	8	0.030
	30	2.2	400	14	0.035
WC346	0	19	280	6	0.021
	6	6	190	8	0.042
	15	1.7	300	9	0.030
	30	0.2	100	5	0.050

Summers J, Mason WS. Proc Natl Acad Sci USA. 2004;101(2):638-640

Limited therapy (4 wks) with Clevudine can induce sustained reductions in WHsAg in WHV chronic carrier woodchucks



Peek SF et al. Hepatology. 2001;33:254-66

Clevudine enhance Immune Clearance

Clevudine Treatment before WHsAg vaccination

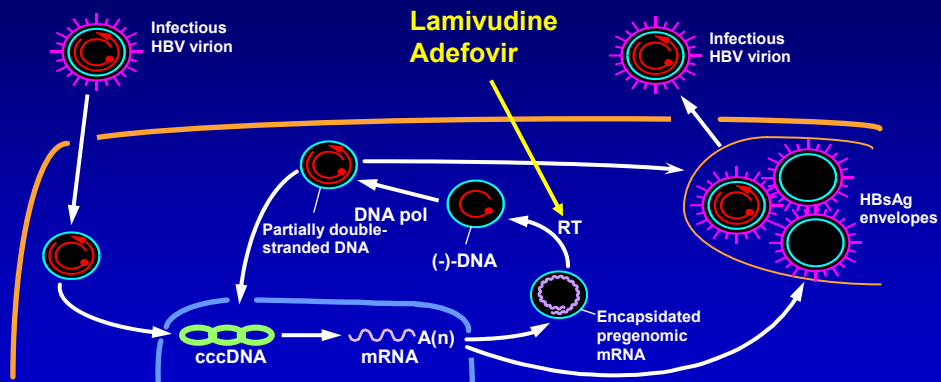
Break Humoral and Cell-Mediated Immune Tolerance

Enhance Cell-Mediated Immunity to WHsAg

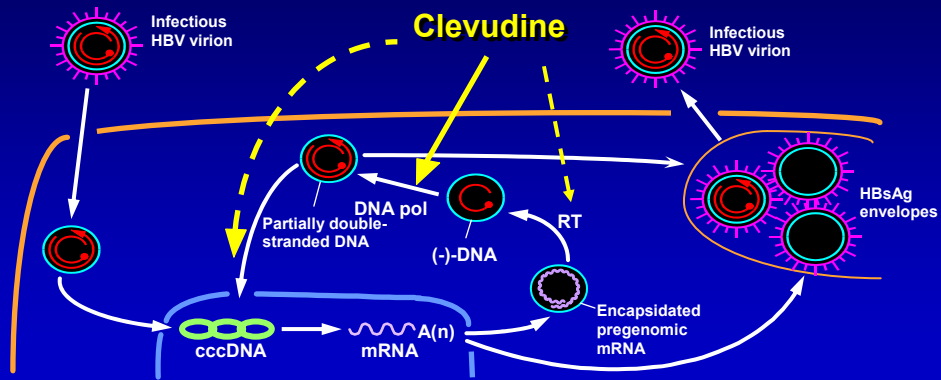
Enhance Cell-Mediated Immunity to Other Viral Antigens

S Menne et al. J. Virol. 76; 5305-5314, 2002

Replication Cycle of Hepatitis B Virus; Mechanism of Action of Lamivudine



Replication Cycle of Hepatitis B Virus and the Mechanism of Action of Clevudine



L-FMAU-302 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
- ◆ Treatment-free follow-up for 24 weeks
- ◆ Multicenter study at 31 sites in Korea

Inclusion and Exclusion Criteria

Inclusion Criteria

- HBsAg positive for > 6 months
- HBeAg negative and Anti-HBe positive
- HBV DNA $\geq 1 \times 10^5$ 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

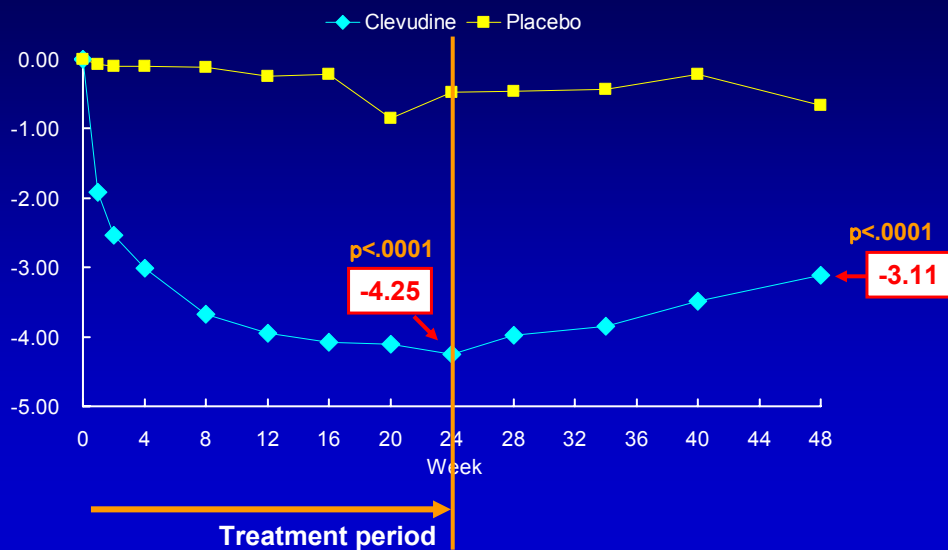
Amplicor PCR assay : <300 copies/mL

- 2) Biochemical improvement – normal ALT

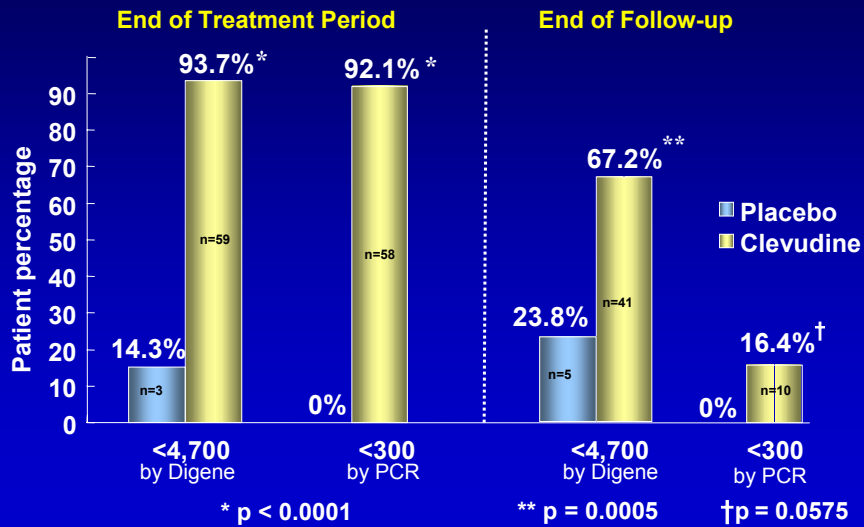
Subject Characteristics at Baseline

	Clevudine 30mg (n=63)	Placebo (n=23)	p-value
Median Age (years)	44	41	0.6974
Gender (n, %)			
Female	11 (17%)	5 (22%)	0.7556
Male	52 (83%)	18 (78%)	
Median HBV DNA (log ₁₀ copies/mL)	6.92	6.37	0.192
Median ALT (IU/L)	112	94	0.7062
Mean ALT (IU/L)(SE)	161.1 (16.5)	149.6 (22.2)	
Genotype C	100%	100%	

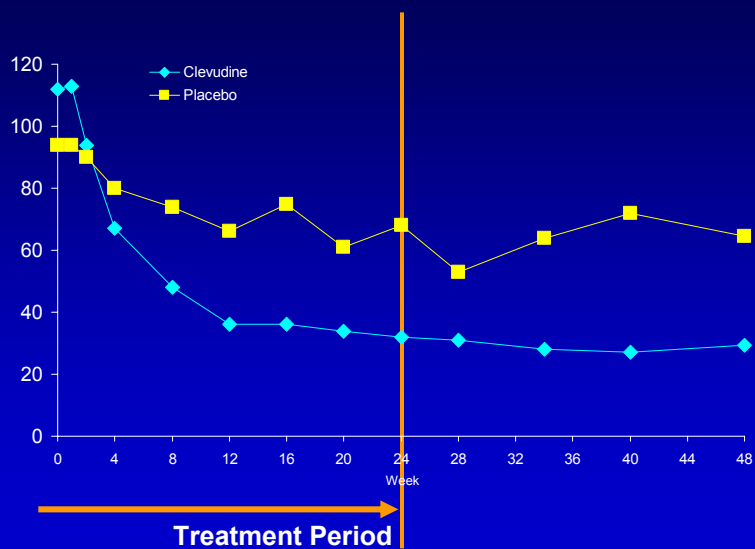
Viral Change (median) from Baseline (log₁₀ copies/mL)



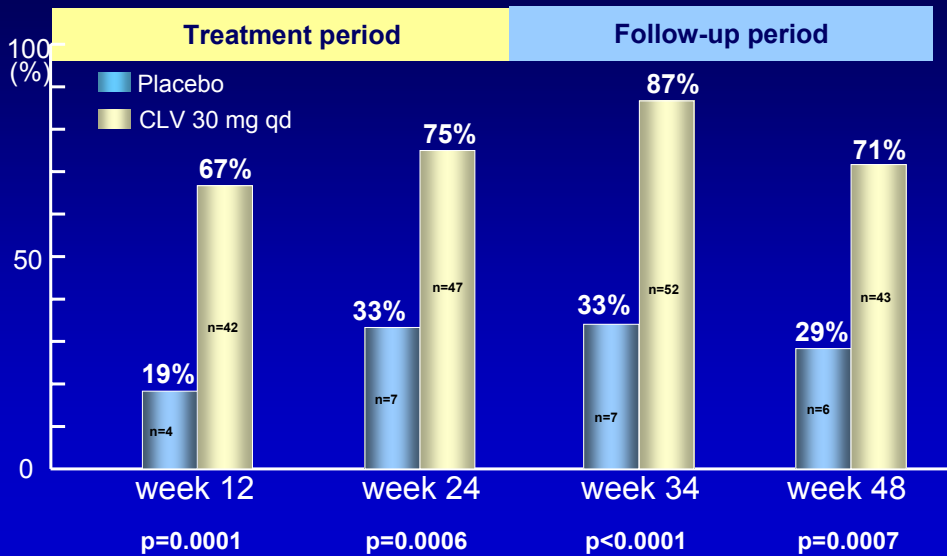
Study 302 Secondary Endpoints Proportion of Patients Achieving Undetectable HBV (copies/mL)



Median ALT Change over Time



Secondary Endpoint Proportion of Patients with Normal ALT in Study 302



Incidence of Adverse Events Most Frequently Reported During the Treatment Period

Adverse Events	Clevudine 30mg n=63 (%)	Placebo n=23 (%)
Infection	9 (14.3)	4 (17.4)
Asthenia	5 (7.9)	2 (8.7)
Abdominal Pain	5 (7.9)	2 (8.7)
Headache	4 (6.4)	0 (0.0)
ALT increased	2 (3.2)	2 (8.7)

Note : This table includes all AEs occurring in more than 5% while on treatment period.
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=63 (%)	Placebo n=23 (%)	p-value
ALT	3 (4.8)	5 (21.7)	0.0292
AST	3 (4.8)	2 (8.7)	0.6066
Bilirubin, Total	1 (1.6)	1 (4.4)	0.4657
Creatine Phosphokinase	1 (1.6)	0 (0)	1
Lipase	1 (1.6)	1 (4.4)	0.4657
Serum Amylase	1 (1.6)	0 (0)	1
Absolute Neutrophils Count	1 (1.6)	0 (0)	1
WBC Count	1 (1.6)	0 (0)	1
Prothrombin time	2 (3.2)	0 (0)	1

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

At the end of the 24 weeks dosing period

- no polymerase mutations at conserved sites of the genome in any patient in clevudine group and placebo group

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