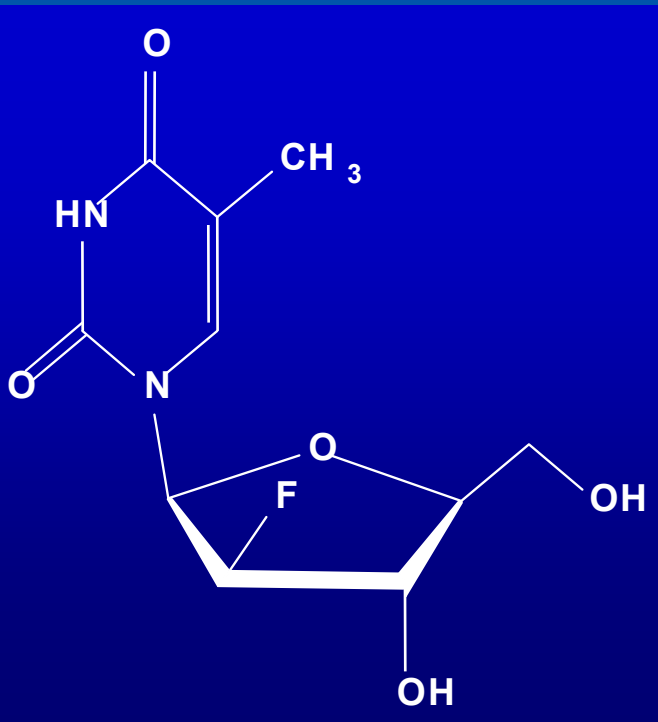


A 48-week clevudine therapy demonstrated significant viral suppression and biochemical improvement in naïve patients with chronic hepatitis B

Young-Hwa Chung¹, KS Lee², JH Kim³, SH Ryu⁴, SW Paik⁵, SH Um⁶, BH Han⁷, M Cho⁸, KS Byun⁶, BI Kim⁵, JW Park⁹, HJ Lee¹⁰, JY Han¹¹, HC Kim¹², SG Hwang¹³, K Yoo¹⁴, YS Lee¹¹, YJ Lee⁴, YS Kim¹⁵, JM Yang¹¹, CY Chon², SH Cho¹¹, YS Kim¹⁶, SK Choi¹⁷, YO Kweon¹⁸, CJ Han¹⁹, JS Hwang²⁰, MS Lee²¹, DG Kim²², HY Lee²³, JY Choi¹¹, HW Yoo²⁴, MJ Otto²⁵, PA Furman²⁵, HS Lee²⁶, BC Yoo⁵

¹AMC ²YUH ³GMS ⁴IUH ⁵SMC ⁶KUH ⁷KMS ⁸PNUH ⁹NCC ¹⁰YUMC ¹¹CUK ¹²WUH ¹³PCUH
¹⁴EWUH ¹⁵IUH ¹⁶SCUH ¹⁷CNUH ¹⁸KNUH ¹⁹KIRMS ²⁰KUDMC ²¹HUH ²²CNUH ²³CUH
²⁴Bukwang Pharm. Co., Ltd. ²⁵Pharmasset Inc. ²⁶SNUH

Clevudine (L-FMAU)



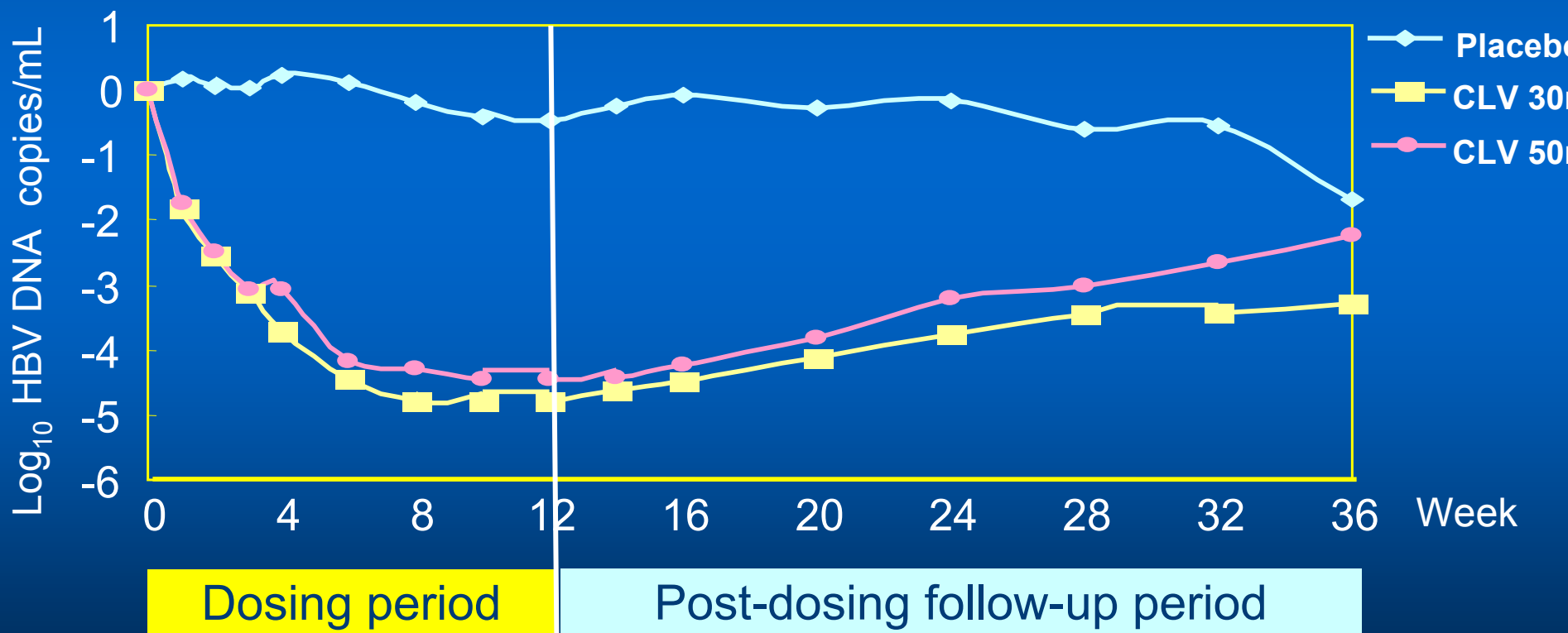
- **Pyrimidine nucleoside analogue**
(L- enantiomer)
- **Potent inhibition of HBV replication**
 - ✓ Inhibition of synthesis of dsDNA from ssDNA
 - ✓ Suppression of cccDNA
- **No cytotoxicity or mitochondrial toxicity**
- Rapid absorption, long half life
- Major route of elimination: renal excretion

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

Clevudine showed potent and durable antiviral activities during a 12-week clevudine therapy in HBeAg-positive CH-B.

Clevudine characteristically induced sustained post-treatment antiviral effects after the 12-week treatment period.

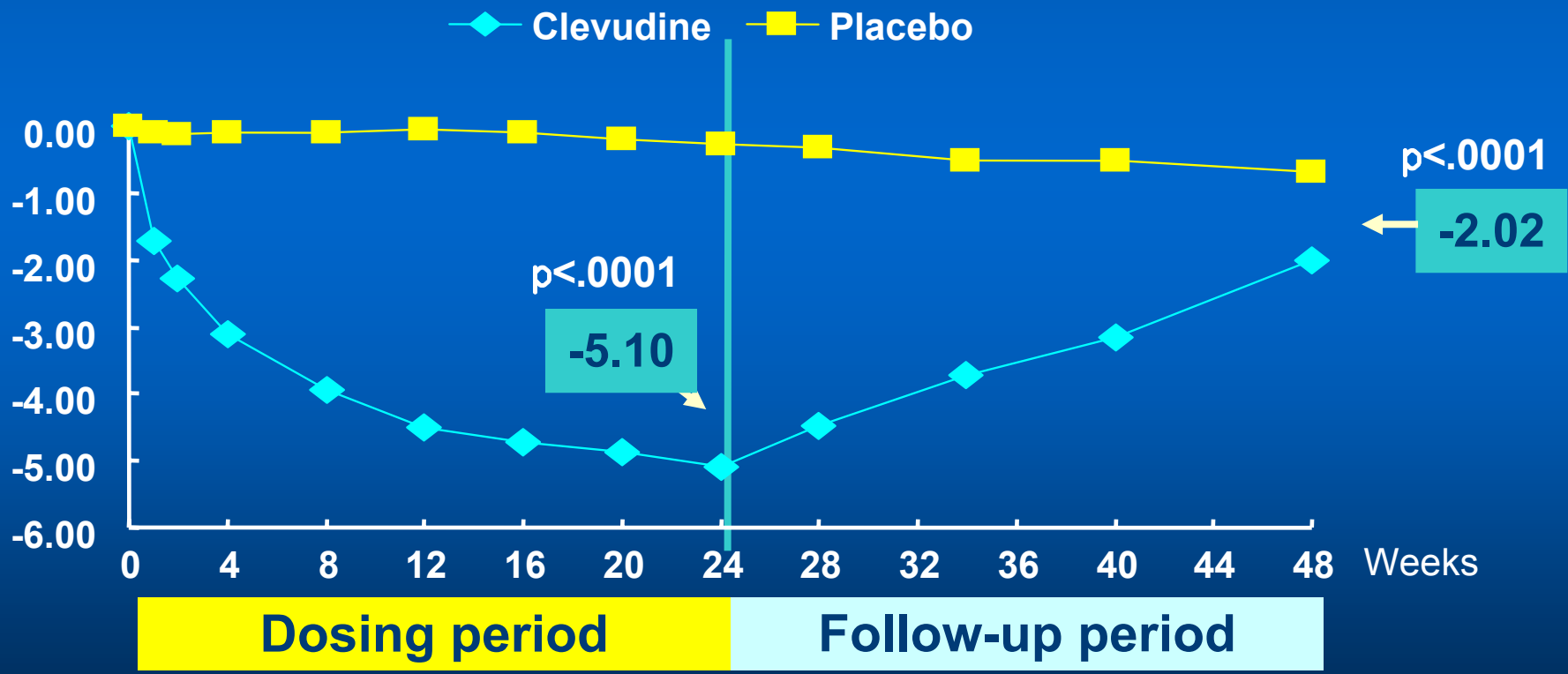
HBV DNA Change (median) from Baseline (\log_{10} copies/mL)



(H-S Lee, Y-H Chung, KS Lee, et al., *HEPATOLOGY*, 2006, in press)






- A 24-week clevudine therapy (30mg QD) was well tolerated and showed potent antiviral activities in HBeAg(+) CHB patients.
- No resistant mutant appeared during the therapy.

HBV-DNA Change (median) from Baseline (log₁₀ copies/mL)



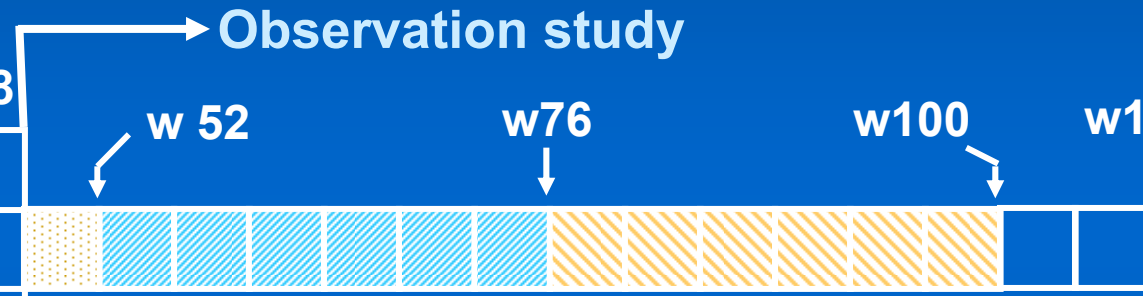
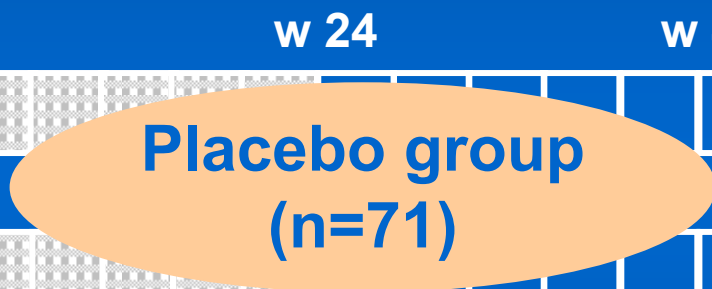
(BC Yoo, JH Kim, KS Lee, et al., presented at 2005 AASLD meeting)

**An open-labelled, phase III,
48-week clevudine trial
in naïve patients
with chronic hepatitis B**

-  Clevudine 30 mg or placebo
-  Clevudine 30 mg
-  Clevudine 10 mg
-  Follow-up without treatment
-  Screening

Complete Response: at 2 consecutive visit
 HBV DNA <4,700 copies/mL
 normal ALT
 HBeAg seroconversion

**A 24-week CLV trial
 In HBeAg(+) CHB (n=220)**



**A 24-week CLV trial
 In HBeAg(-) CHB (n=82)**

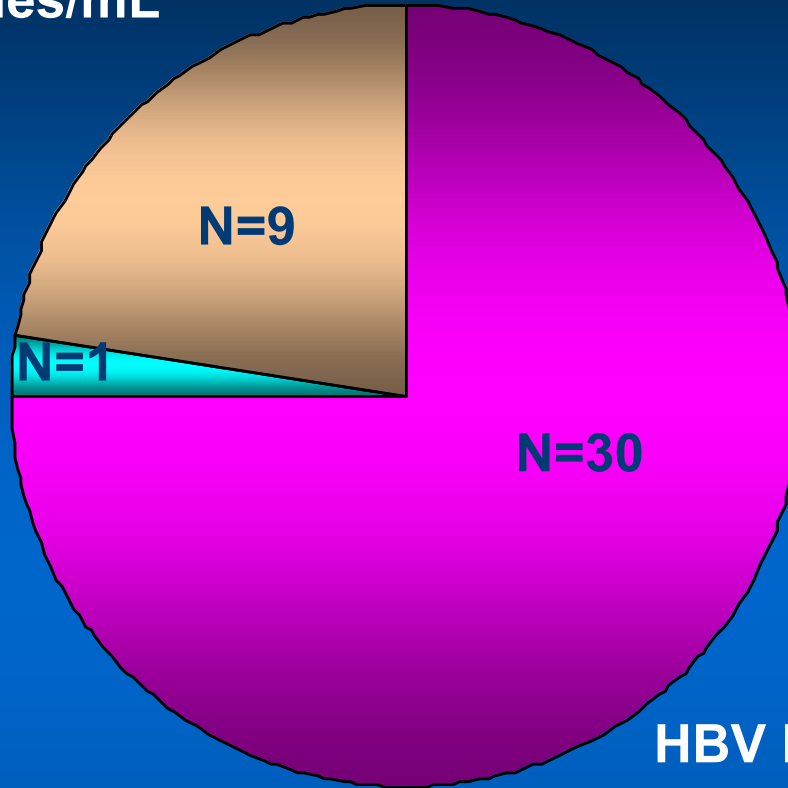


Complete Response:
 HBV DNA <4,700 copies/mL
 normal ALT

A 48-week trial in Naïve patients
 [n=55; HBeAg(+): n=40, HBeAg(-): n=15]

HBV DNA >4,700 copies/mL
Normal serum ALT

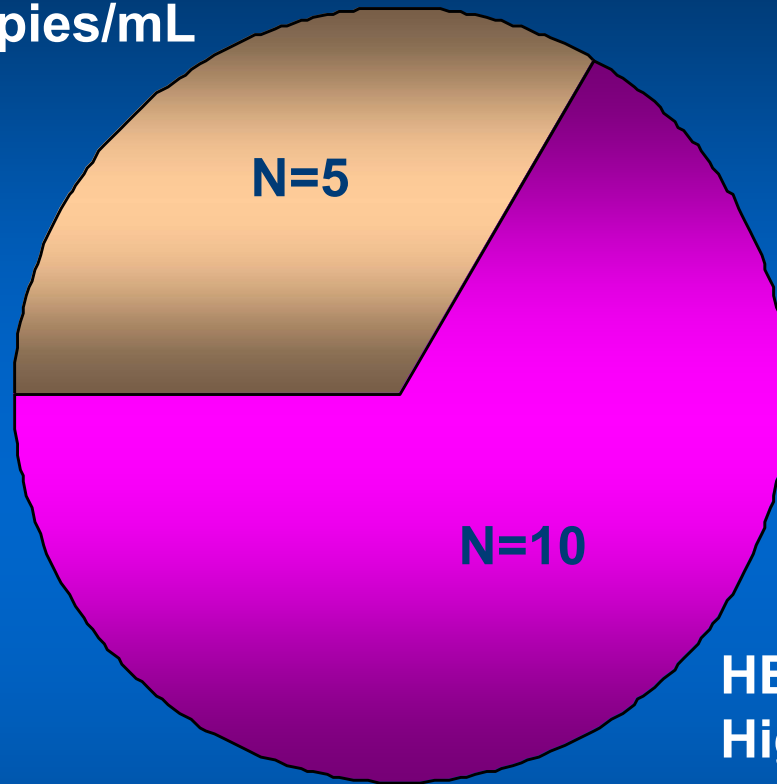
HBV DNA <4,700 copies/mL
Normal serum ALT



HBV DNA >4,700 copies/mL
High serum ALT

**Baseline Characteristics of Naïve HBeAg+ CHB Patients
Treated with Clevudine for 48 weeks (N=40)**

**HBV DNA >4,700 copies/mL
Normal serum ALT**



**HBV DNA >4,700 copies/
High serum ALT**

**Baseline Characteristics of Naïve HBeAg- CHB Patients
Treated with Clevudine for 48 weeks (N=15)**

Inclusion and Exclusion Criteria of 24-week Clevudine Therapy

Inclusion Criteria

- HBV DNA levels $\geq 10^6$ copies/mL
- Serum ALT level: 2 to 10 times of ULN

Exclusion Criteria

- HIV or HCV seropositivity
- Hepatocellular carcinoma or decompensated LC
- Other significant associated diseases in other organs
- Breastfeeding and pregnant women
- Previous treatment with any nucleoside analogue

Methods

1. Measurement of serum HBV-DNA

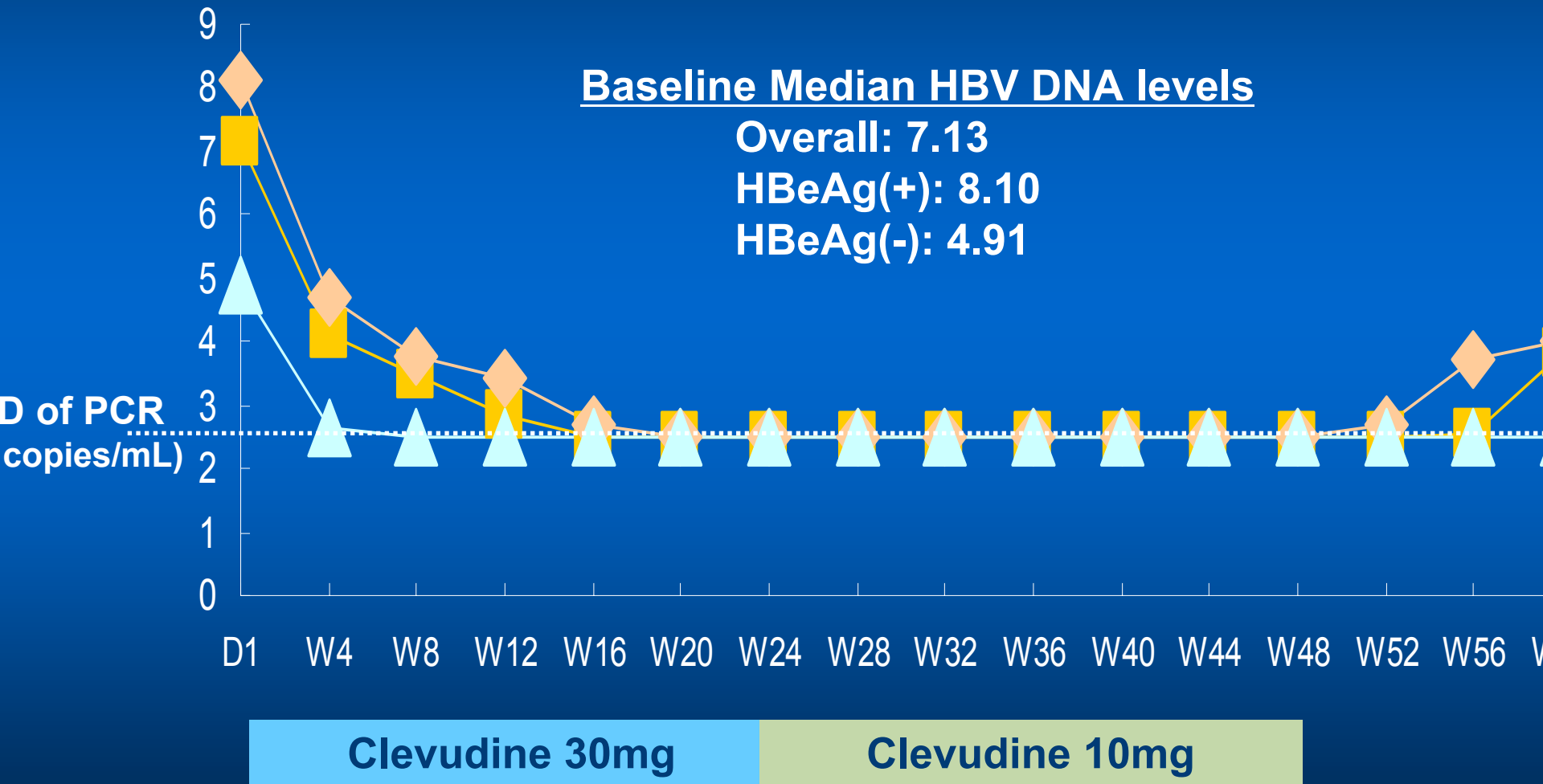
- Digene Ultra-sensitive Hybrid Capture II HBV DNA test
 - ; From baseline to the end of the study.
 - ; Lower LOD of 4,700 copies/mL
- COBAS Amplicor HBV monitor test
 - ; When HBV DNA levels reduced to <4,700 copies/mL
 - ; Lower LOD of 300 copies/mL

2. Determination of HBeAg and Anti-HBe

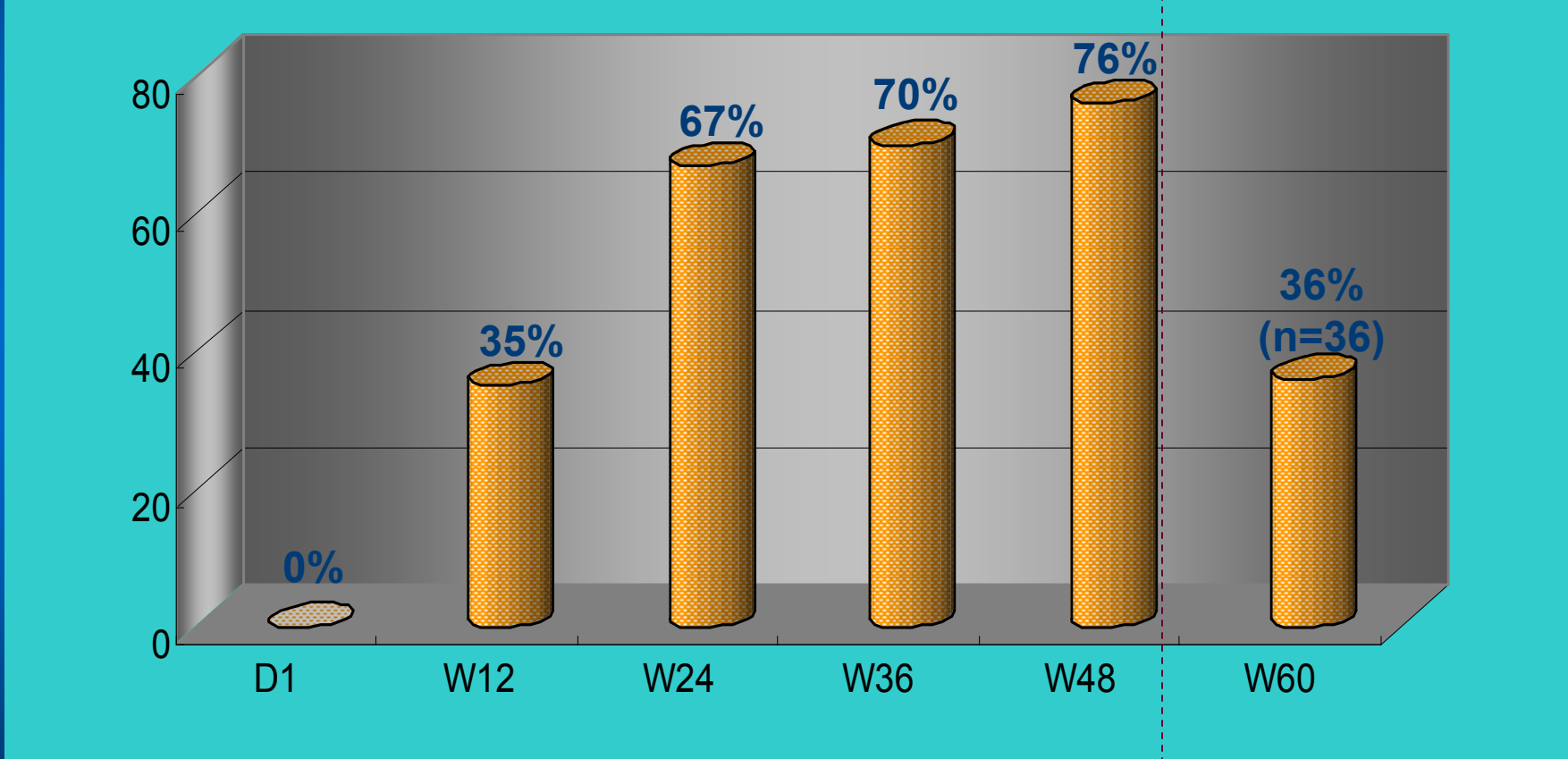
- Radioimmunoassay (Abbott Laboratories, North Chicago, IL)

3. Serum ALT level

Median Serum HBV DNA Levels Over Time (log₁₀ copies/mL)



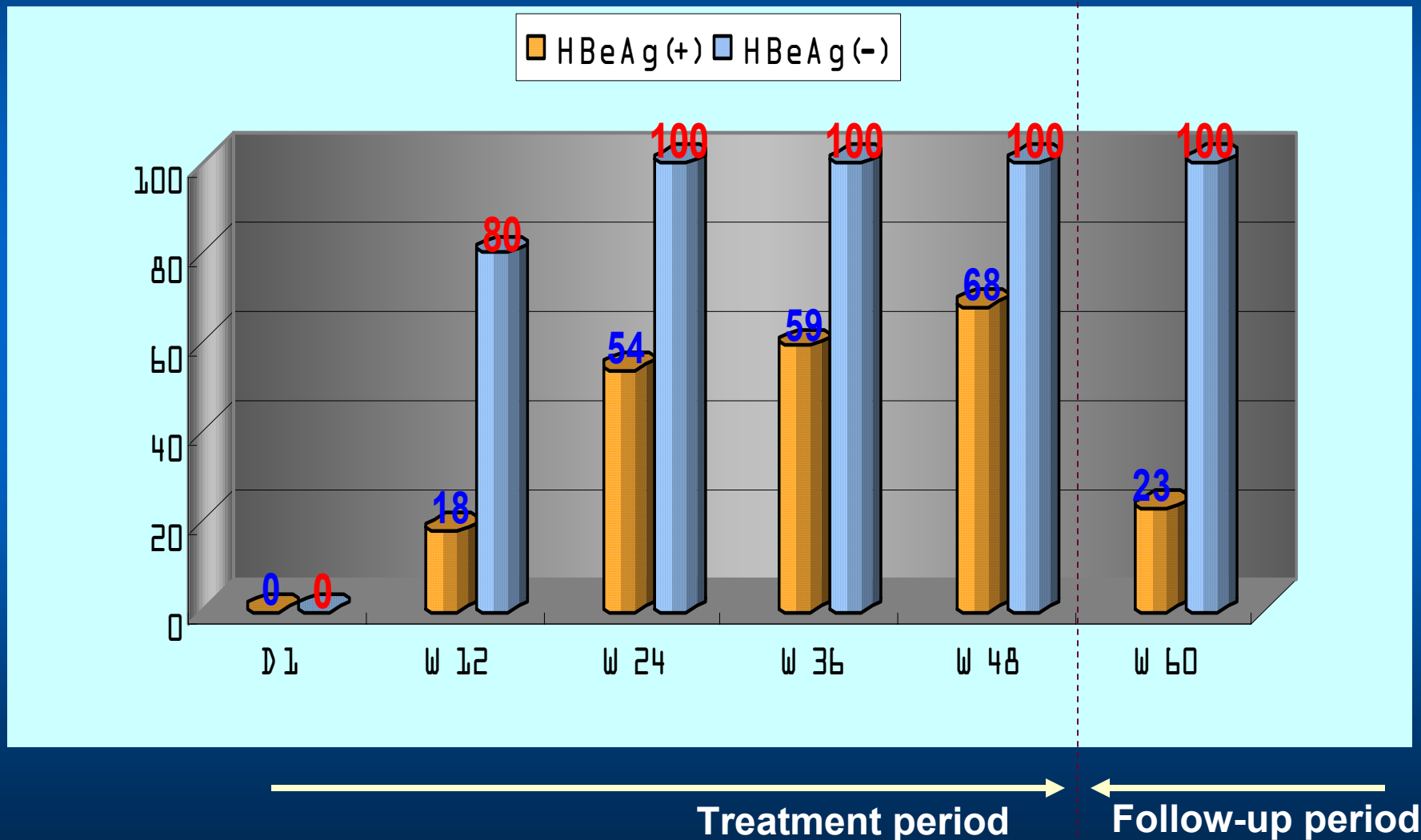
Overall Proportion of Patients with HBV DNA <300 copies/mL (Detection limit of Amplicor PCR) (n=55)



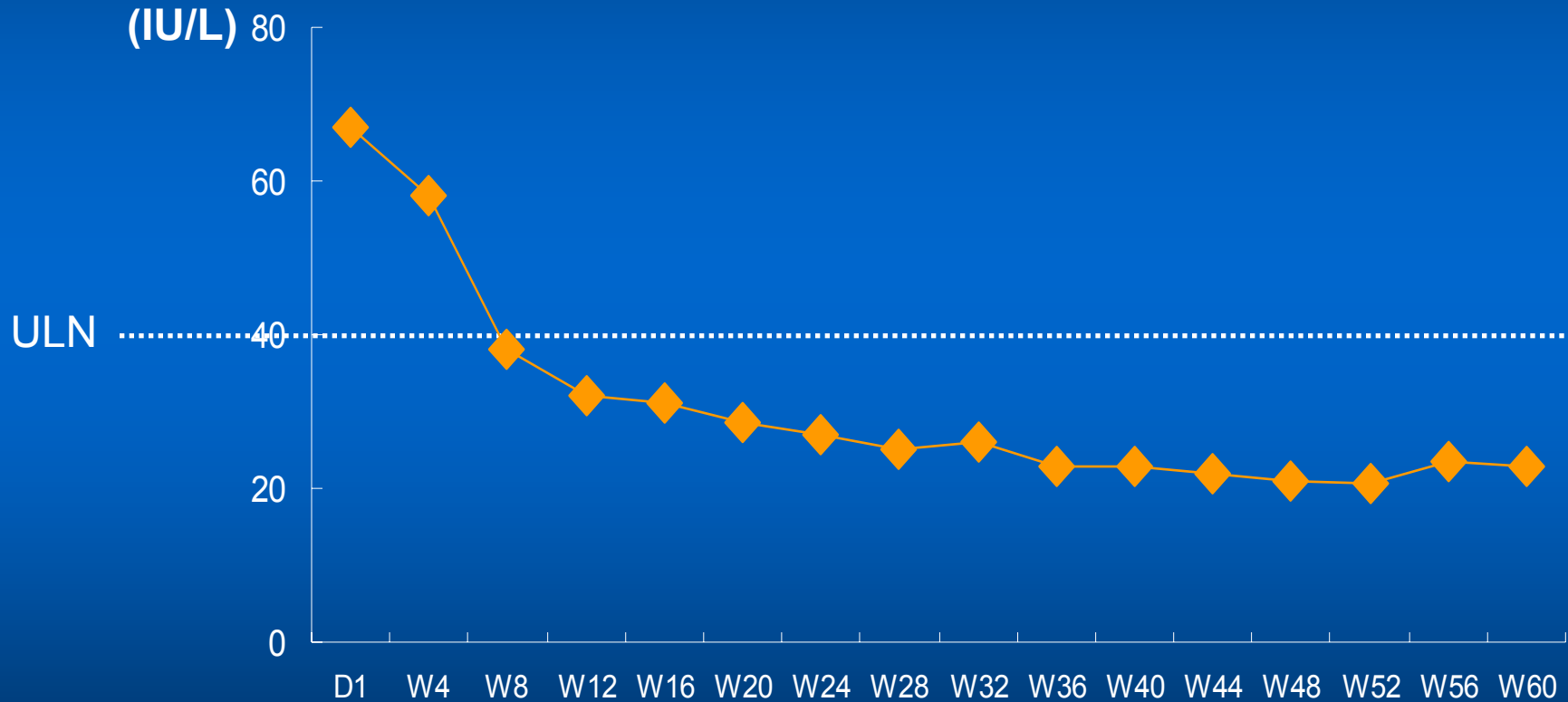
Treatment period

Follow-up period

Proportion of Patients with HBV DNA <300 copies/mL (Detection limit of Amplicor PCR)



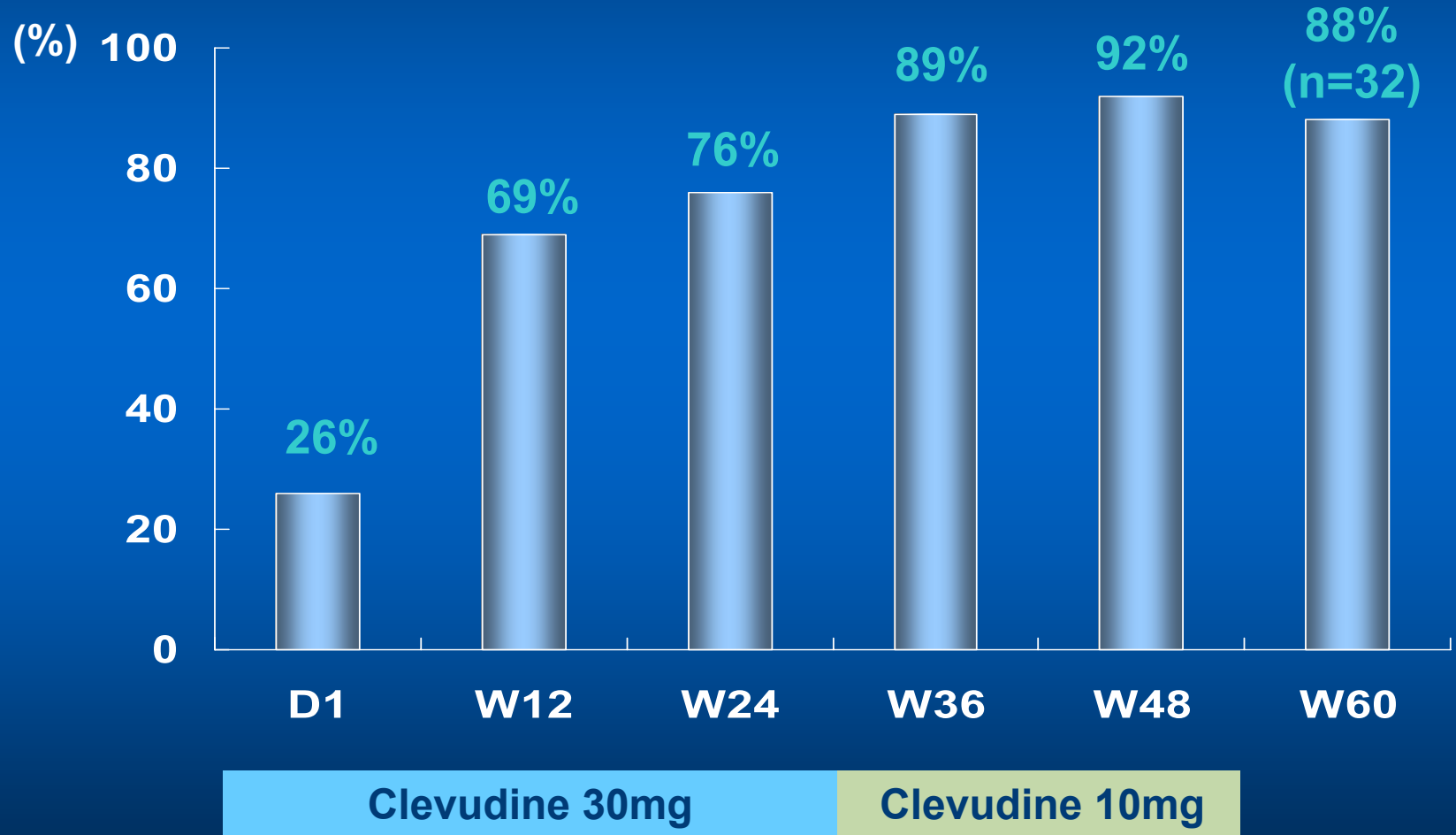
Median Serum ALT Levels Over Time (n=55)



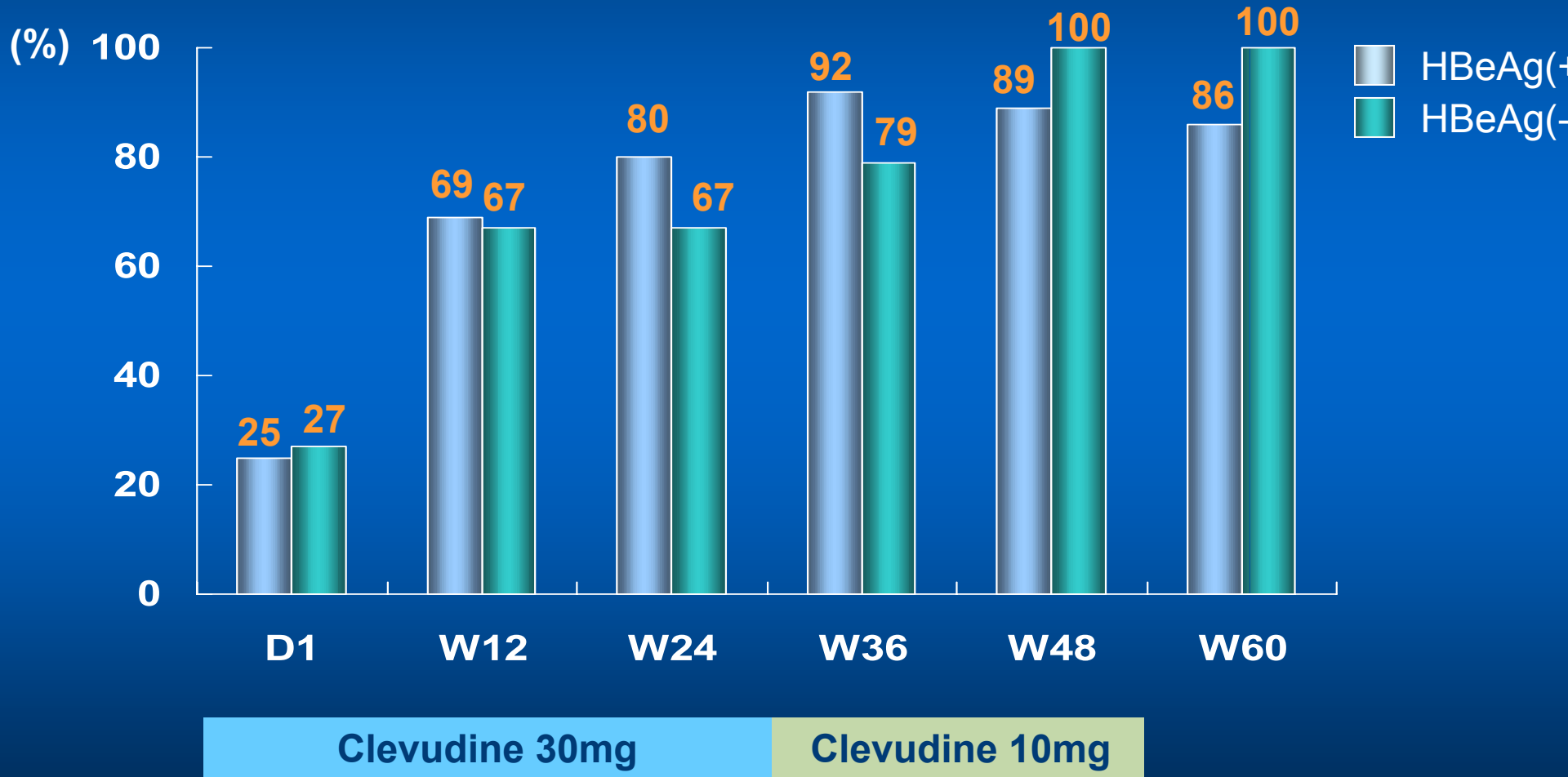
Clevudine 30mg

Clevudine 10mg

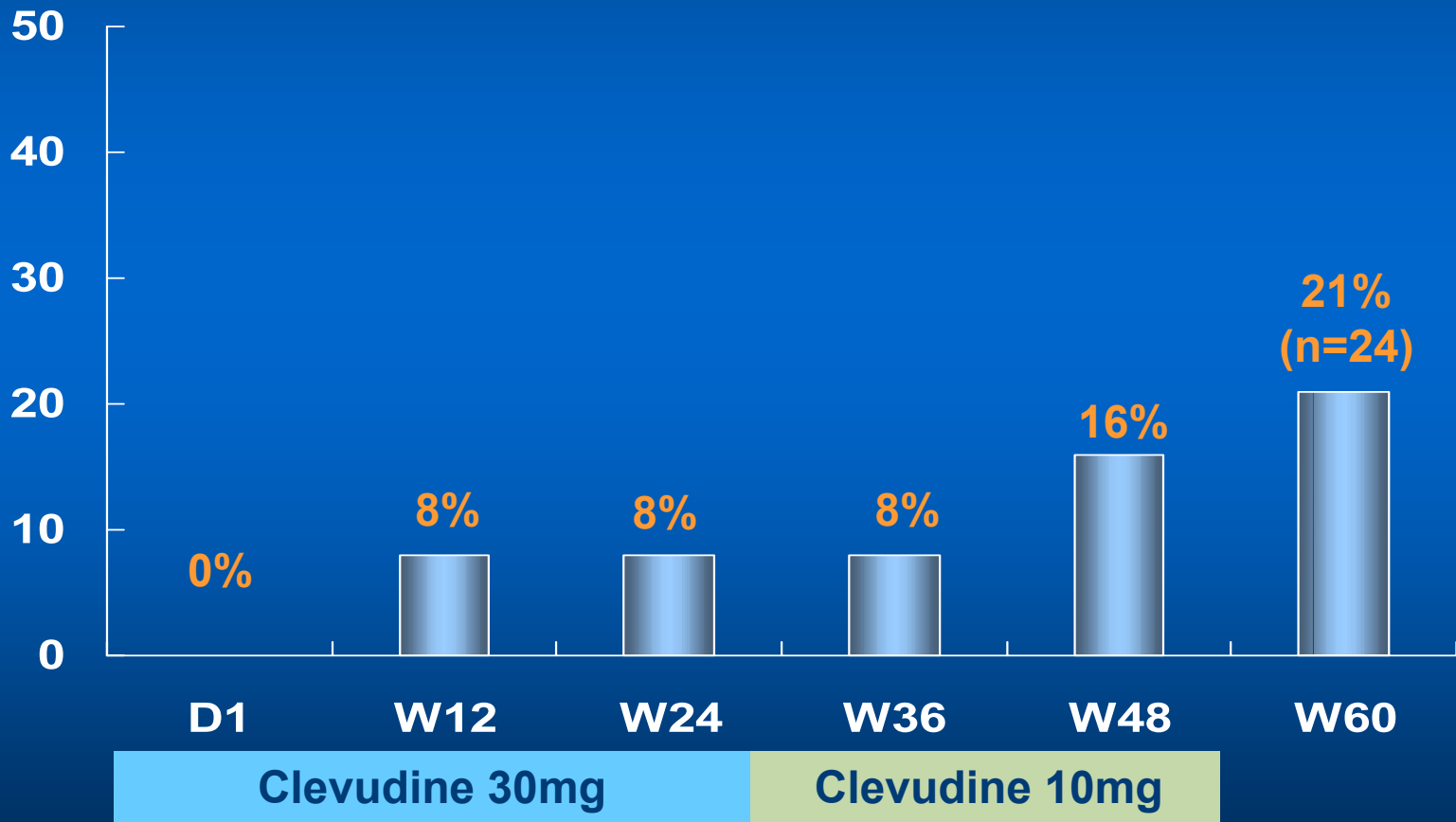
Overall Proportion of Patients with Normal Serum ALT Level (n=55)



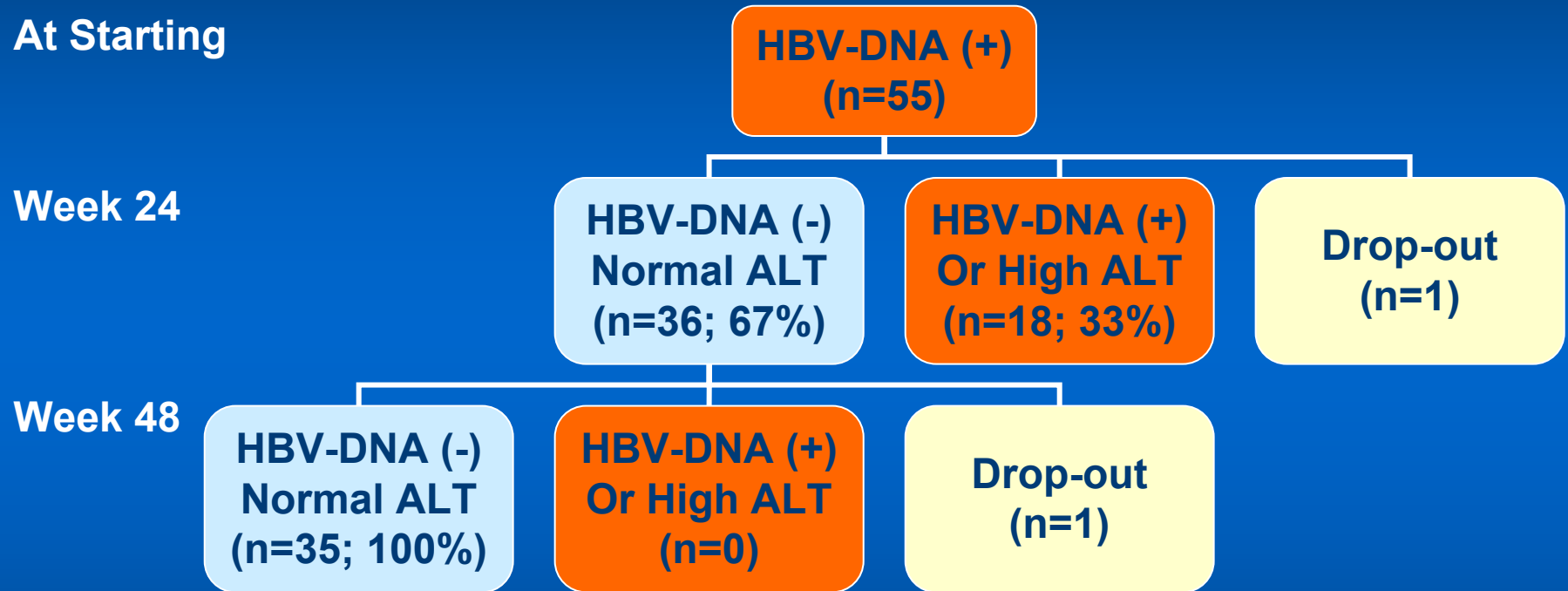
Proportion of Patients with Normal Serum ALT Level



Loss of Serum HBeAg following 48-week Clevudine therapy (n=40)



Sustained Effects During Maintenance Therapy In Patients with Undetectable serum HBV-DNA by PCR



All the patients who achieved negative HBV DNA by PCR at the week 24 showed sustained viral and biochemical responses during the maintenance therapy with lower dose.

Clinical Adverse Events during 48-week Clevudine Therapy (N=55)

Adverse Events*	Number
Myalgia	5
Diarrhea	4
Abdominal Pain	4
Anorexia/Nausea	3
Pruritus	2
Rash	2

* All the adverse events were mild and transient

Summaries

- A 48-week clevudine therapy demonstrated significant viral suppression and biochemical improvement in naïve patients with chronic hepatitis B.
- Clevudine showed sustained antiviral effect after the cessation of therapy.
- All the patients who achieved negative HBV-DNA by PCR at the week 24 showed sustained viral and biochemical responses during the maintenance therapy with lower dose.
- No serious adverse event was observed during the 48-week clevudine therapy.

Conclusion

Clevudine may have promising potentials as a safe and effective antiviral agent for the treatment of chronic HBV infection.

Thanks for Your Attention!



Have a Nice Day!

Young-Hwa Chung M.D.