Long-Term Histological Improvement with Entecavir (ETV) Therapy in Patients with Chronic Hepatitis B (CHB) from Japanese and Worldwide Development Programs

YF Liaw[1], TT Chang[2], SS Wu[3], ER Schiff[4], KH Han[5], CL Lai[6], R Safadi[7], SS Lee[8], W Halota[9], ZD Goodman[10], H Zhang[11], U Iloeje[11], S Beebe[11], B Kreter[12], H Ishikawa[13], Y Katano[14], K Takaguchi[15], M Omata[16]

1. Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan. 2. National Cheng Kung University Medical College, Tainan, Taiwan. 3. Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan. 4. University of Miami Hospital & Clinics, Miami, FL, USA. 5. Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea. 6. Department of Medicine, Queen Mary's Hospital, University of Hong Kong, Hong Kong, China. 7. Division of Medicine, Hadassah Medical Center, Jerusalem, Israel. 8. Liver Unit, University of Calgary, Calgary, AB, Canada. 9. Klinika Chorob Zakaznych AM, Bydgoszcz, Poland. 10. Armed Forces Institute of Pathology, Washington, WA, USA. 11. Research & Development, Bristol-Myers Squibb Company, Wallingford, CT, USA. 12. Research & Development, Bristol-Myers Squibb Company, Princeton, NJ, USA. 13. Research & Development, Bristol-Myers KK, Tokyo, Japan. 14. Department of Gastroenterology, Graduate School of Medicine, Nagoya University, Aichi, Japan. 15.Department of Internal Medicine, Kagawa Prefectural Central Hospital, Kagawa, Japan. 16. Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

Introduction

- Entecavir (ETV) demonstrated potent suppression of HBV DNA, biochemical and histologic improvement through 48 weeks in nucleoside-naïve and lamivudine-refractory (LVDr) patients in both the Japanese and Global study programs[1-4]
- We present histologic results from cohorts in the Japanese and Global program who received ETV for up to 6 years and had evaluable baseline and long-term biopsies

1. Chang TT, et al. N Engl J Med 2006; 354:1001-10
2. Lai CL, et al. N Engl J Med 2006;354:1010-20
3. Kobashi H, et al. J Gastroenterol Hepatol 2008;24:255-61
4. Suzuki F, et al. J Gastroenterol Hepatol 2008;23:1320-6

Endpoints for Long-term Histology Cohorts

- Endpoints presented will be compared to baseline

- Japanese Program:
  - Change in Knodell necroinflammatory and fibrosis score
  - Histologic improvement (≥2-point decrease in Knodell necroinflammatory score)
  - Improvement in fibrosis score (≥1-point decrease in Knodell fibrosis score)
  - Resistance analysis

- Global Program:
  - Change in Knodell necroinflammatory score and Ishak fibrosis score
  - Histologic improvement (≥2-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score)
  - Improvement in Ishak fibrosis score (≥1-point decrease)

Japanese Long-term Histology Cohorts

Japanese Study Population

- The Long-term Histology Cohorts from Japan consist of patients who:
  - were initially treated with ETV in studies ETV-053 or ETV-052
  - subsequently enrolled in ETV-060
  - had biopsies from three time points: baseline, Week 48 and Week 148

Nucleoside-naïve

	Baseline	Week 48 - 52	Week 100	Week 148
ETV 0.1 mg	n =32	n =32	n =32	n =31
ETV 0.5 mg	n =34	n =34	n =33	n =33

Lamivudine-refractory

	Baseline	Week 48 - 52	Week 100	Week 148
ETV 0.5 mg	n =41	n =40	n =37	n =30
ETV 1.0 mg	n =43	n =42	n =38	n =35

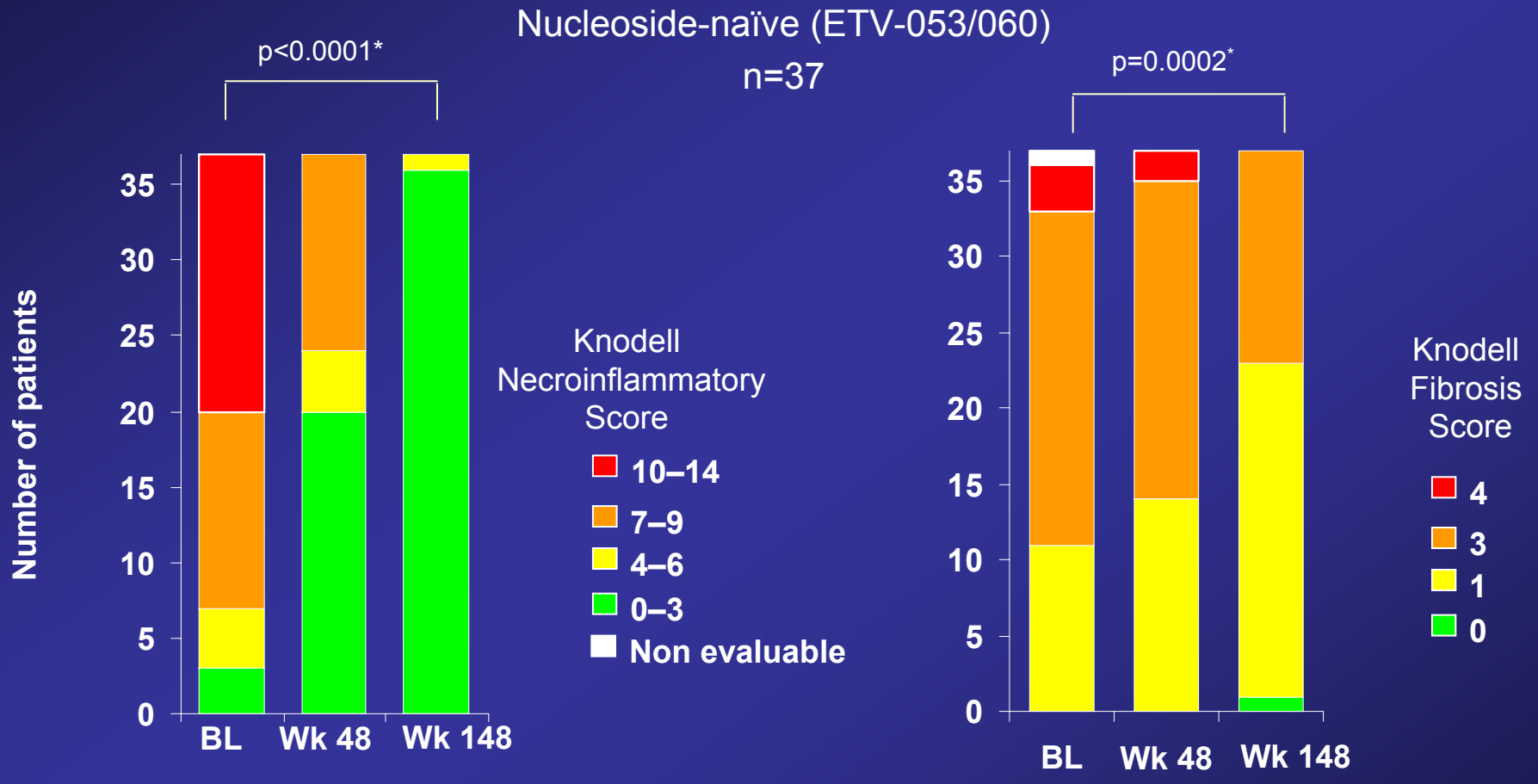
Japan Long-term Histology Cohorts: Baseline Demographics and Disease Characteristics

	Nucleoside-naive ETV-053/060 n=37*	LVD-refractory ETV-052/060 n=27*
Age, mean (years)	44	44
Male, n (%)	29 (78)	24 (89)
HBeAg(+), n (%)	28 (76)	18 (67)
HBV DNA by PCR log_{10} copies/mL, mean (SD)	7.24 (1.03)	7.87 (0.77)
ALT, IU/L, mean (SD)	155 (194)	122 (80)
Knodell HAI score, mean (SE)	9.0 (0.48)	6.2 (0.60)
Knodell fibrosis score, mean (SE)	2.5 (0.17)	2.6 (0.18)
HBV genotype C, n (%)	37 (100)	27 (100)

*Patients with biopsies at baseline, Week 48, and Week 148

HAI = histologic activity index

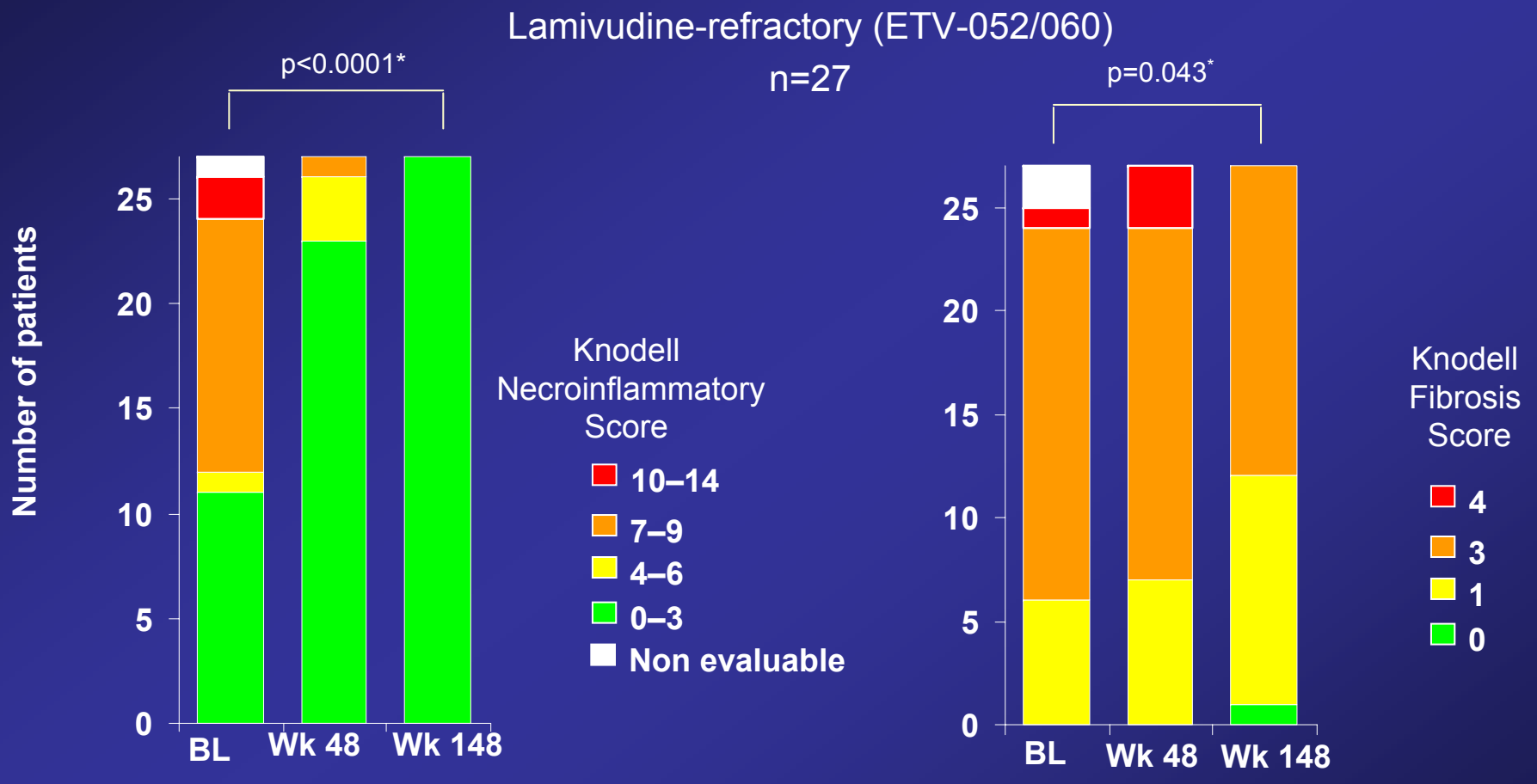
Japanese Nucleoside-Naïve Patients
Distribution of Knodell Necroinflammatory and Fibrosis Scores at Baseline, Week 48 and Week 148



- **100% of patients achieved a ≥ 2 point improvement in Knodell necroinflammatory score**
- **47% of patients achieved a ≥ 1 point decrease in Knodell fibrosis score**
- **95% of patients had undetectable HBV DNA <400 copies/mL at Week 148**

* Wilcoxon signed rank test

Japanese Lamivudine-Refractory Patients
Distribution of Knodell Necroinflammatory and Fibrosis Scores at Baseline, Week 48 and Week 148



- **Cumulative resistance rate was 36% in the overall LVDr patient population studied**
- **89% of patients achieved a ≥ 2 point improvement in Knodell necroinflammatory score**
- **32% of patients achieved a ≥ 1 point decrease in Knodell fibrosis score**
- **56% of patients had undetectable HBV DNA <400 copies/mL at Week 148**

* Wilcoxon signed rank test

Resistance

- Nucleoside-naïve patients (ETV-053/060)
  - Up to Week 148, 5/37 patients had HBV DNA ≥400 copies/mL
  - One of five patients had evidence of genotypic ETVr substitutions* with virologic breakthrough. However, both Knodell necroinflammatory and fibrosis scores of this patient were improved at Week 148

- LVDr patients (ETV-052/060)
  - Up to Week 148, 14/27 patients had HBV DNA ≥400 copies/mL
  - Six of fourteen patients had evidence of genotypic ETVr substitutions*
    - Five of six patients had improvement in Knodell necroinflammatory score at Week 148
    - Knodell fibrosis scores at Week 148 were available for five of the patients:
      - two patients showed improvement and three patients showed no worsening in fibrosis scores

* ETV resistance substitutions = LVDr (M204V/I ± L180M) + substitution at one of the following residues: T184, S202 or M250

Global Long-term Nucleoside-Naïve Histology Cohort

Global Study Population
Efficacy Evaluable Histology Cohort (n=57)

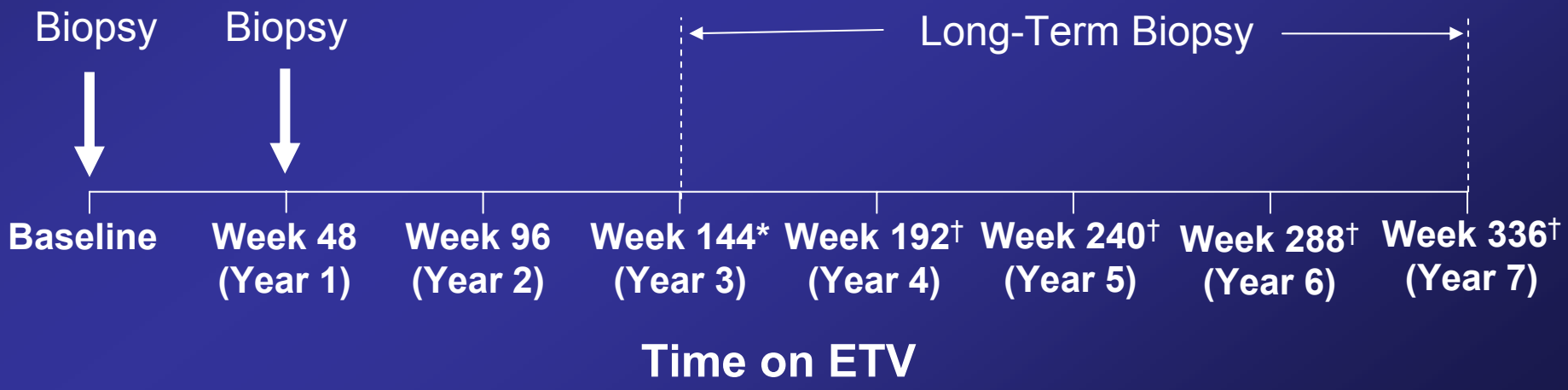
Nucleoside-naïve patients from:

ETV-022 HBeAg(+)

ETV-027 HBeAg(-)

Subset of 901 rollover study

- **Minimum of 3 years ETV therapy**
- **Adequate baseline and long-term biopsies**
- **Baseline Knodell necroinflammatory score of ≥2**

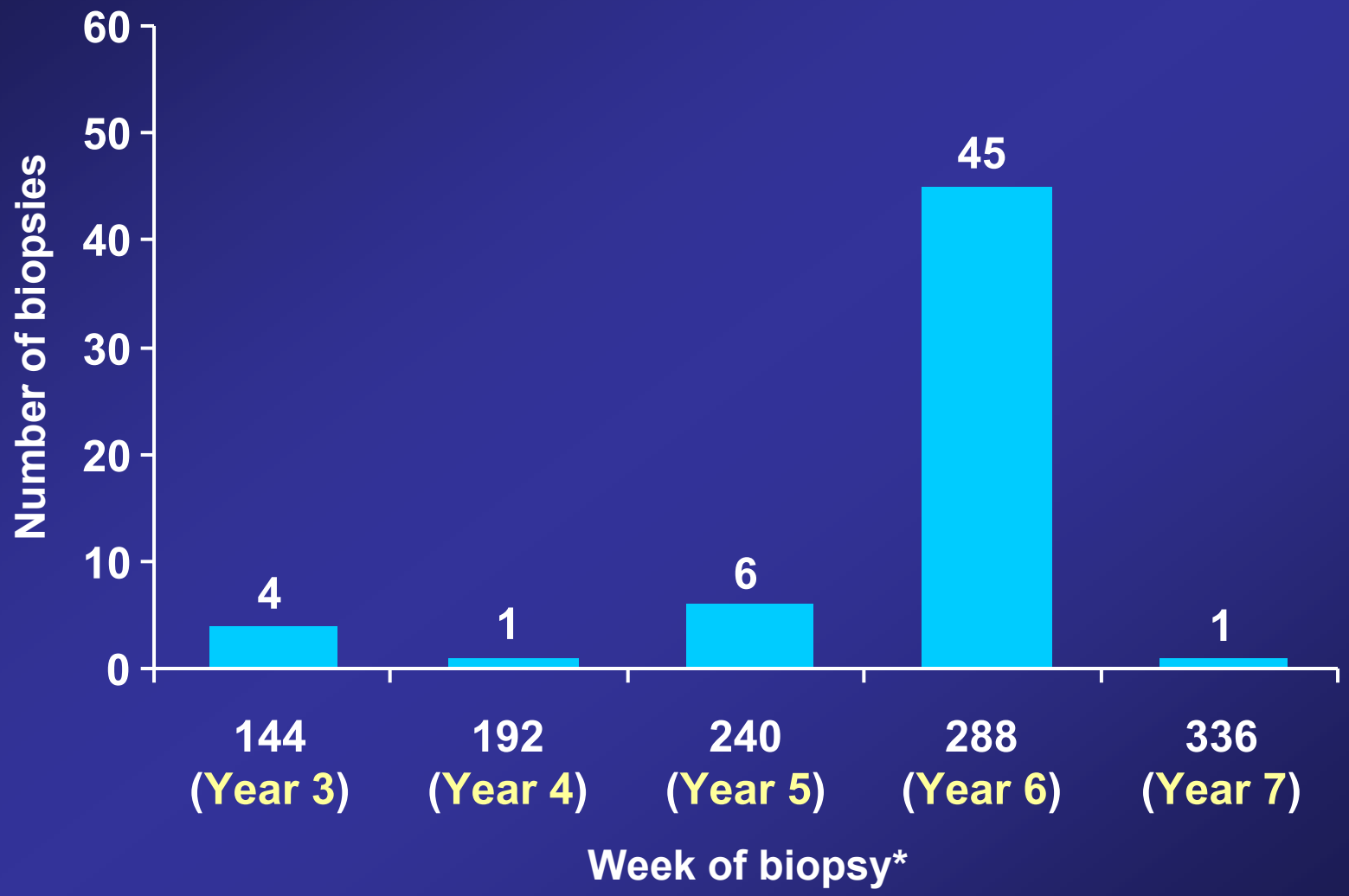


*Week 144 (+24 weeks)
† (±24 weeks)

Global Long-term Histology Cohort: Demographics and Baseline Characteristics

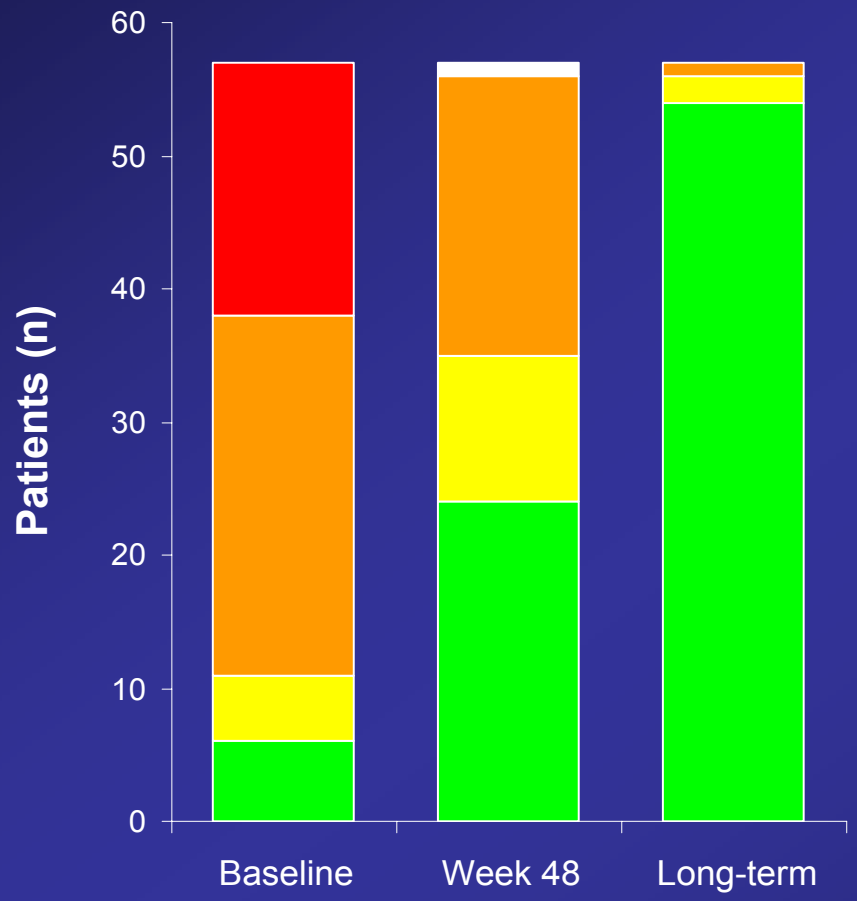
	Efficacy Evaluable Cohort (n=57)
Age, mean (years)	40
Male (%)	82
Race:	
Asian (%)	67
Non-Asian (%)	33
HBeAg(+) (%)	72
HBV DNA by PCR, mean (log_{10} copies/mL)	9.4
ALT, mean (U/L)	142
Knodell NI score, mean	7.98
Ishak fibrosis score, mean	2.44
HBV genotype (%)	

Global Long-term Histology Cohort: Distribution of Biopsies (n=57)



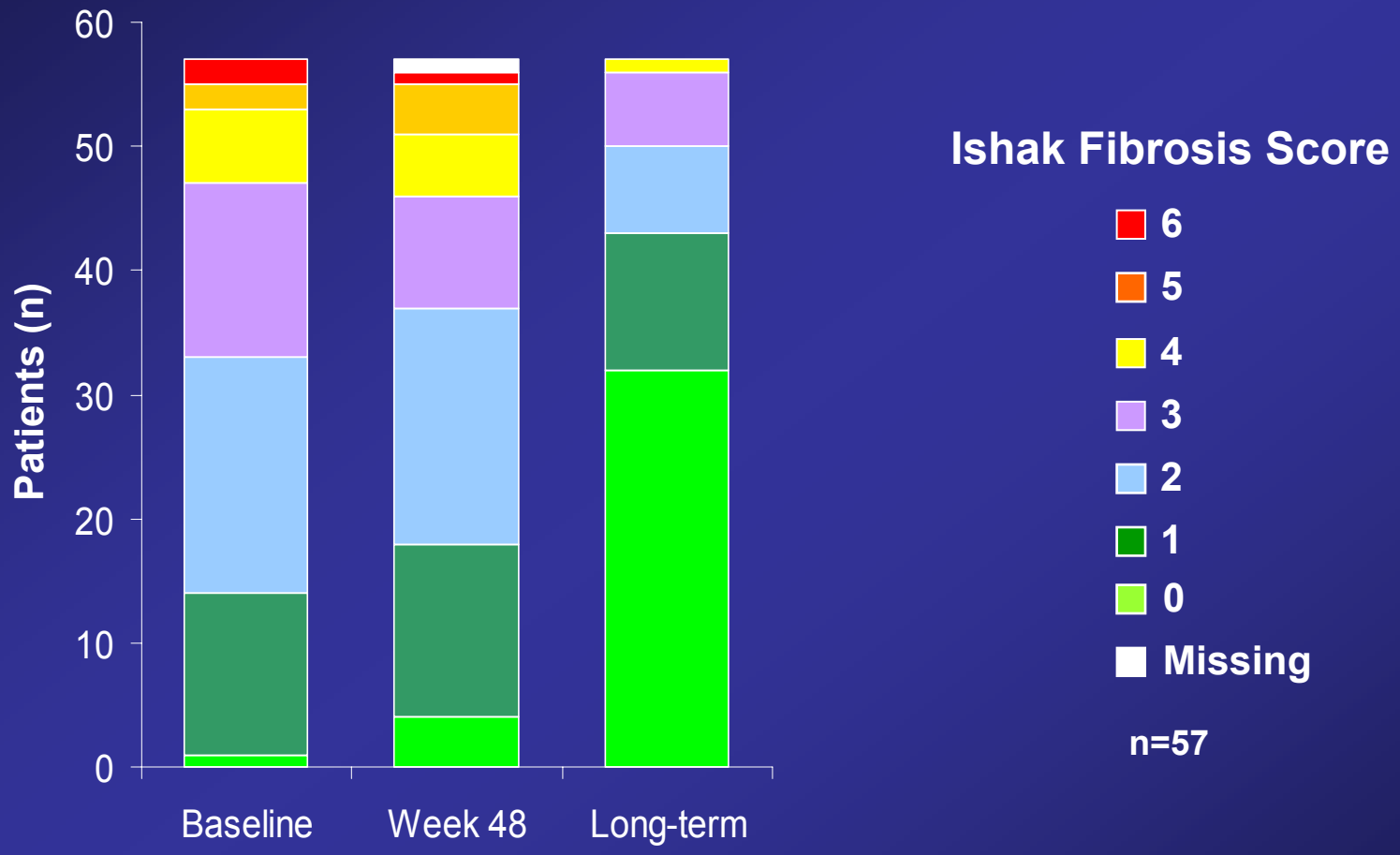
* The Weeks represent windows during which the biopsies were performed, the number represents the mid-point of each window

Global Long-term Histology Cohort: Distribution of Knodell Necroinflammatory Scores at Baseline, Year 1, and Years 3–7



- **96% of patients achieved a ≥ 2 point improvement in Knodell necroinflammatory score with no worsening in fibrosis**
- **100% of patients had HBV DNA <300 copies/mL at time of long-term biopsy**

Global Long-term Histology Cohort Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Years 3–7



- **88% of patients had a ≥ 1 point decrease in Ishak fibrosis score**
- **Four cirrhotic patients, demonstrated at least a 1-point improvement in Ishak fibrosis score (median change: 3-point decrease), see poster #W1808**

Summary of Results

- Treatment with ETV beyond 48 weeks resulted in further improvement in necroinflammatory and fibrosis scores
  - Japanese Program through 3 yrs of ETV therapy:
    - 100% and 89% of naïve and LVDr patients, respectively had ≥ 2 point decrease in Knodell necroinflamatory score
    - High proportions of the naïve and LVDr patients achieved HBV DNA suppression during 3 years of ETV
  - Global program, median of 6 yrs of ETV therapy:
    - 96% of naïve-patients achieved histologic improvement
    - 100% of naïve-patients achieved undetectable HBV DNA at time of long-term biopsy
    - Safety profile was consistent with previously reported experience

Conclusion

The results from these two independent cohorts demonstrate that long-term entecavir treatment results in durable suppression of viral replication and regression of fibrosis/cirrhosis