Hepatitis B Medications

Lamivudine (*Epivir-HBV*)

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Lamivudine (3TC)
Summary of Key Studies

- Phase 3 Trials
  - BeHOLD (HBeAg+): ETV versus 3TC in HBeAg-Positive
  - BeHOLD (HBeAg-): ETV versus 3TC in HBeAg-Negative
  - GLOBE: Lamivudine versus Telbivudine
  - PegINF alfa-2a versus Lamvivudine verus Both (HBeAg+)
  - PegINF alfa-2a versus Lamvivudine verus Both (HBeAg-)
  - Long-term Lamivudine and Impact on Advanced Fibrosis

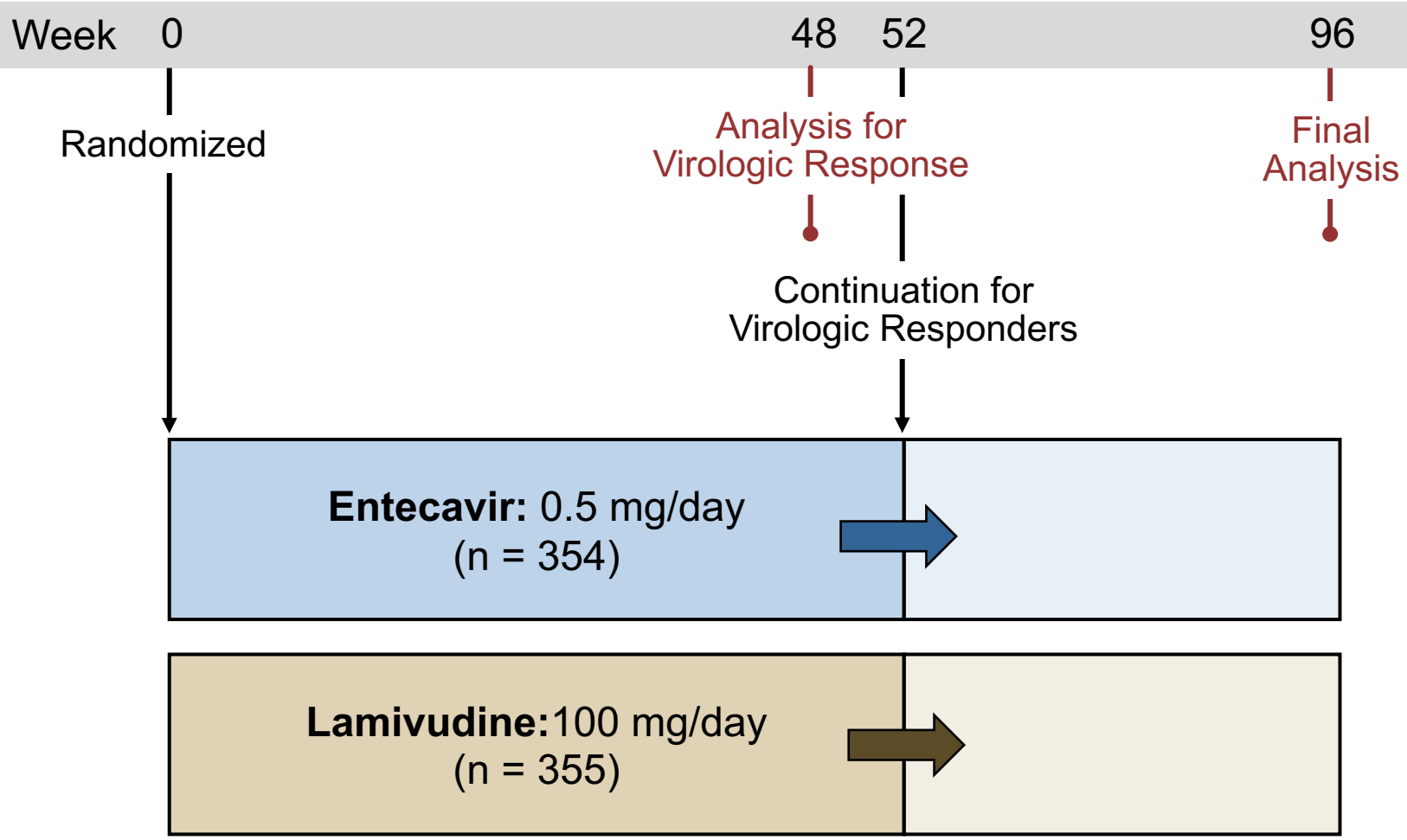
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD: HBeAg-Positive, Week 48

Entecavir versus Lamivudine: 48 Week Data BEHoLD (HBeAg-Positive): Study Design

- **Background**
  - Phase 3, randomized, double-blind controlled trial
  - 137 centers in Americas, Asia, Australia, Europe, & Middle East
- **Subjects (n = 709)**
  - Age ≥16 years with documented HBeAg-positive
  - Excluded: prior nucleoside/nucleotide active against HBV >12 weeks
  - Excluded: coinfection with HIV, HCV, or HDV
- **Regimens**
  - Entecavir: 0.5 mg once daily (n = 354)
  - Lamivudine: 100 mg once daily (n = 355)
- **Study End-Points**
  - Primary: hepatic histologic improvement
  - Secondary: changes in HBV DNA, HBeAg seroconversion, normalization of ALT

Source: Chang TT, et. al. N Engl J Med. 2006;354:1001-10.

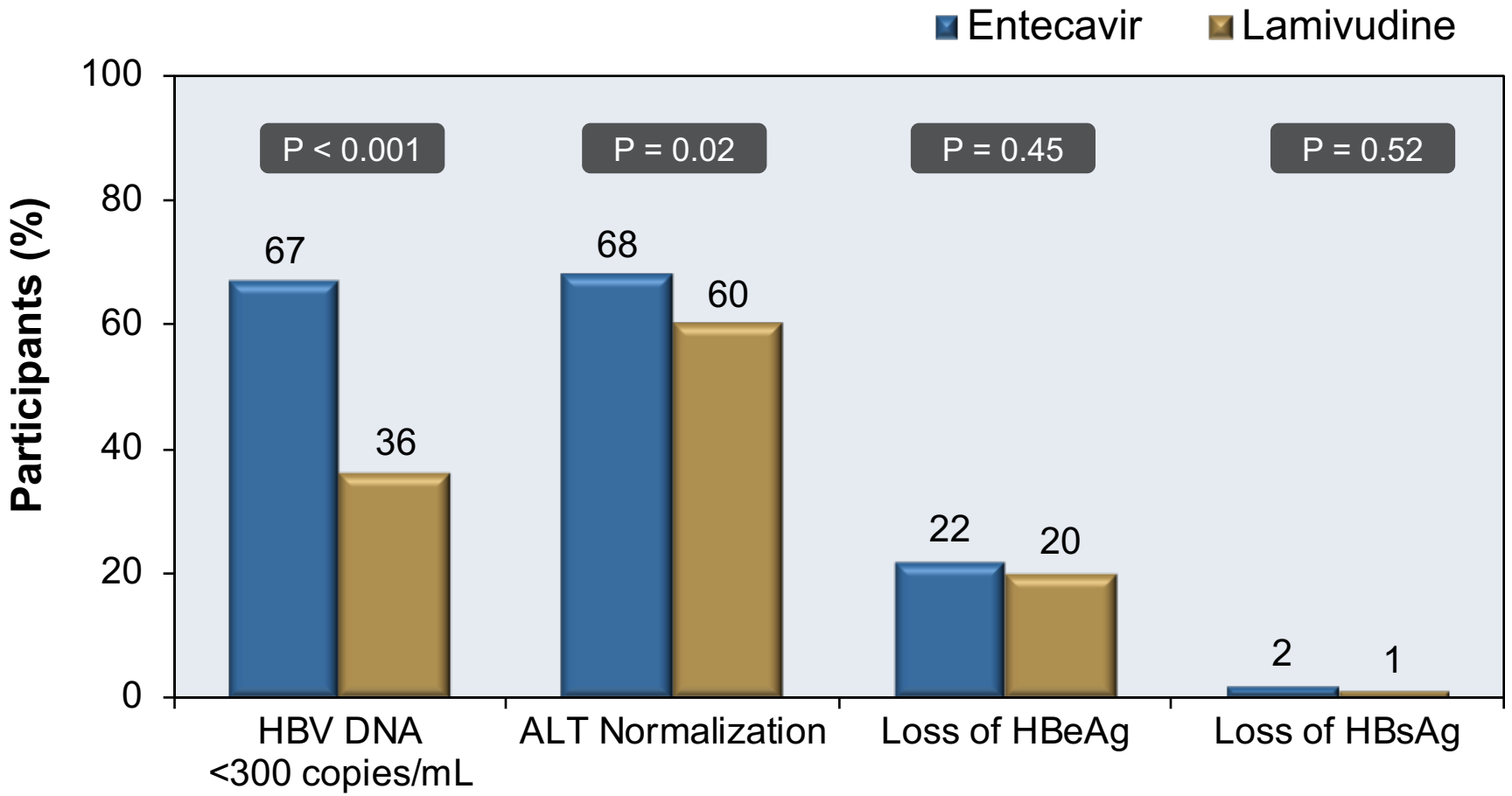
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Positive): Study Design



Source: Chang TT, et. al. N Engl J Med. 2006;354:1001-10.

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Positive): Results

HBeAg-Positive Study Participants: Week 48 Treatment Response



Source: Chang TT, et. al. N Engl J Med. 2006;354:1001-10.

Entecavir versus Lamivudine: 48 Week Data BEHoLD (HBeAg-Positive): Conclusions

Conclusions: “Among patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic, and biochemical improvement are significantly higher with entecavir than with lamivudine. The safety profile of the two agents is similar, and there is no evidence of viral resistance to entecavir.”

Source: Chang TT, et. al. N Engl J Med. 200;354:1001-10.

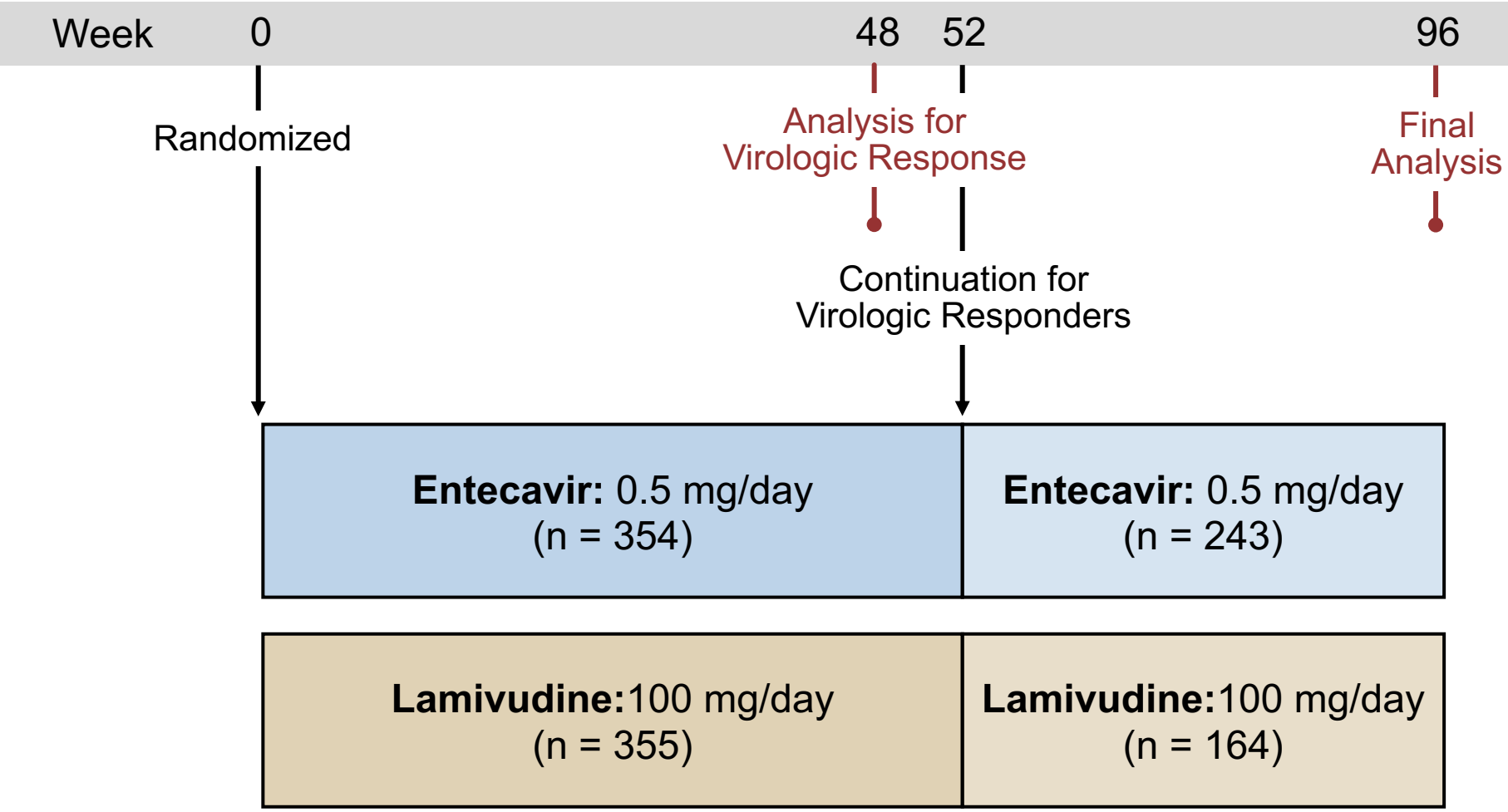
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD: HBeAg-Positive, Week 96

Entecavir versus Lamivudine: 96 Week Data BEHoLD (HBeAg-Positive): Conclusions

- **Background**
  - Phase 3, randomized, double-blind controlled trial
  - 146 centers in Europe, Asia, Americas, Australia & Middle East
- **Subjects**
  - N = 715 with chronic HBeAg-positive
  - Excluded: prior lamivudine therapy x >12 weeks or any prior entecavir
  - Week 52 “virologic responders” (HBV DNA to <700,000 copies/mL & HBeAg loss): continue blinded treatment to week 96
- **Regimens**
  - Entecavir 0.5 mg once daily
  - Lamivudine 100 mg once daily
- **Study End-Points**
  - Virologic Response: HBV DNA level <300 copies/mL
  - Serologic Response: HBeAg seroconversion, HBsAg loss

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.

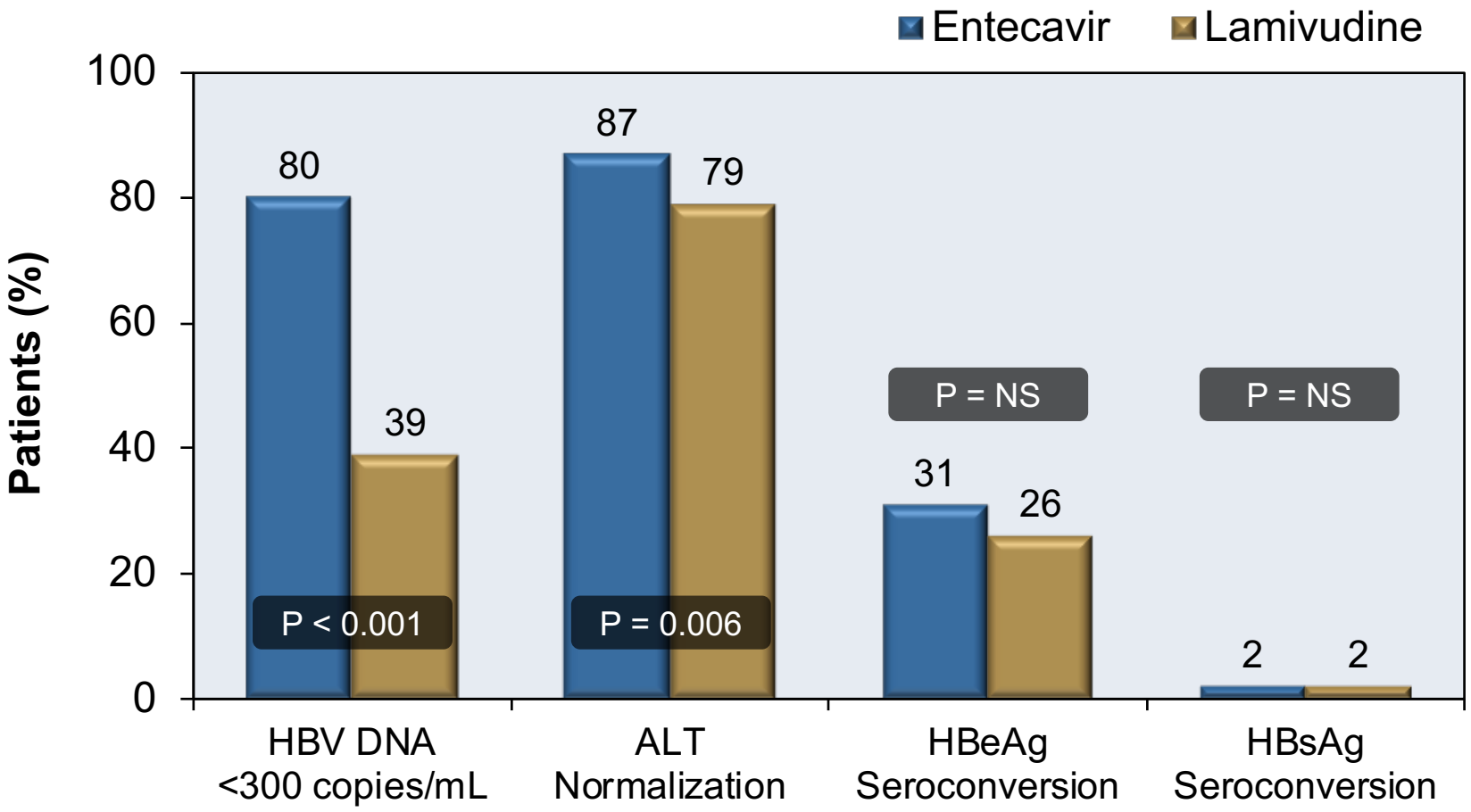
Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Study Design



Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.

Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Results

HBeAg-Positive Study Participants: Week 96 Treatment Response



Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.

Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Safety & Adverse Events

Baseline Characteristic	Entecavir (n = 354)	Lamivudine (n = 355)
Any adverse event ≥5%, % Headache Fatigue Increased ALT levels	 10 6 4	 8 5 7
Serious adverse event, %	8	8
Adverse event leading to discontinuation, no.	1	9
Lab abnormalities, no. (%) Grade 4 ALT (>10x ULN) and >2x baseline	 12* (3)	 23** (7)

*11 of 12 of these flares resolved within 1-7 weeks. 11 of 12 were also associated with ≥2 log10 decline in HBV DNA
**11 of 23 associated with increasing HBV DNA level that preceded or coincided with the flare

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.

Entecavir versus Lamivudine: 96 Week Data BEHoLD (HBeAg-Positive): Conclusions

Conclusions: “Entecavir treatment through 96 weeks results in continued benefit for patients with HBeAg-positive chronic hepatitis B.”

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.

Entecavir versus Lamivudine in HBeAg-Negative

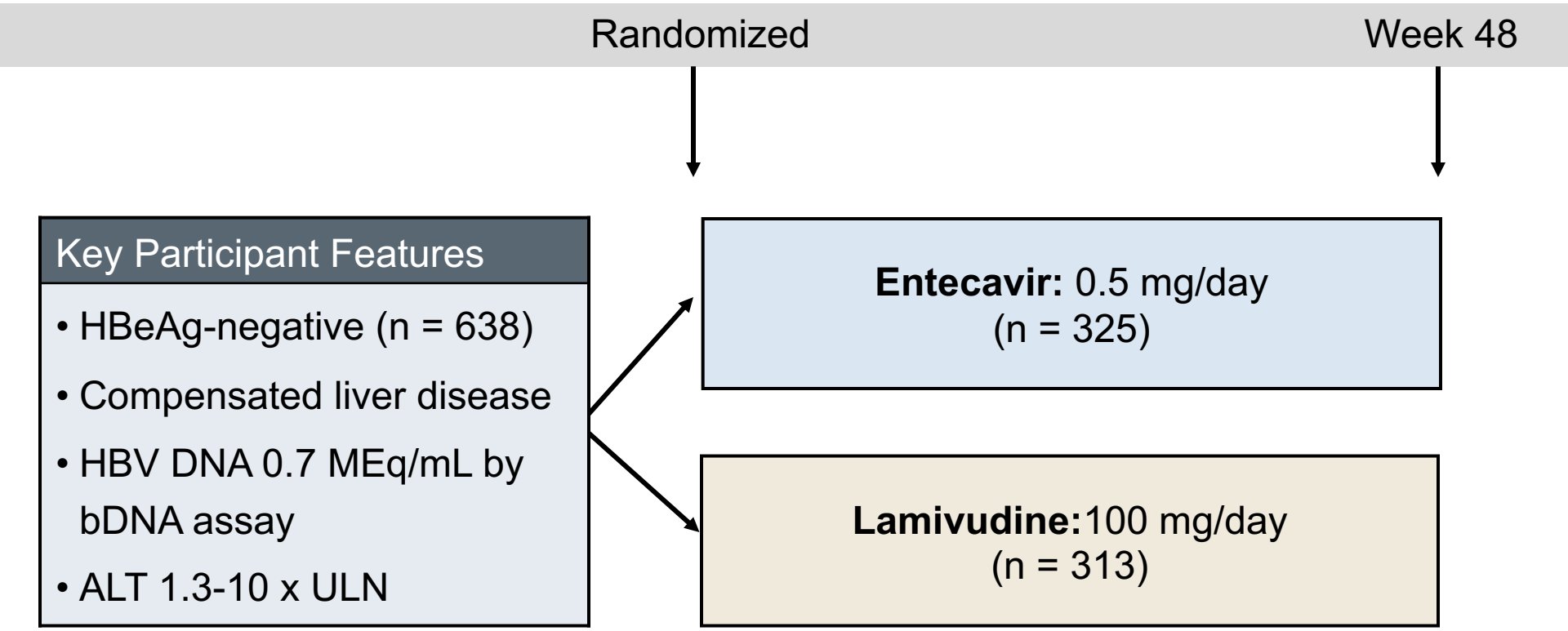
BEHoLD: HBeAg-Negative

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Negative): Study Design

- **Background**
  - Phase 3, randomized double-blind controlled trial
  - 146 centers in Europe, Asia, Americas, Australia & Middle East
- **Subjects**
  - N = 638 with chronic HBeAg-negative
  - Excluded: prior lamivudine therapy >12 weeks or any prior entecavir
- **Regimens**
  - Entecavir 0.5 mg QD (n = 325)
  - Lamivudine 100 mg QD (n = 313)
- **Study End-Points at week 48**
  - Primary: Histologic improvement (≥2 points on Knodell necroinflammatory score, and no worsening on Knodell fibrosis score)
  - Secondary: HBV DNA < 300 copies/ml; decrease in Ishak fibrosis score; normalization of ALT

Source: Lai C, et. al. N Engl J Med. 2006;354:1011-20.

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Negative): Study Design



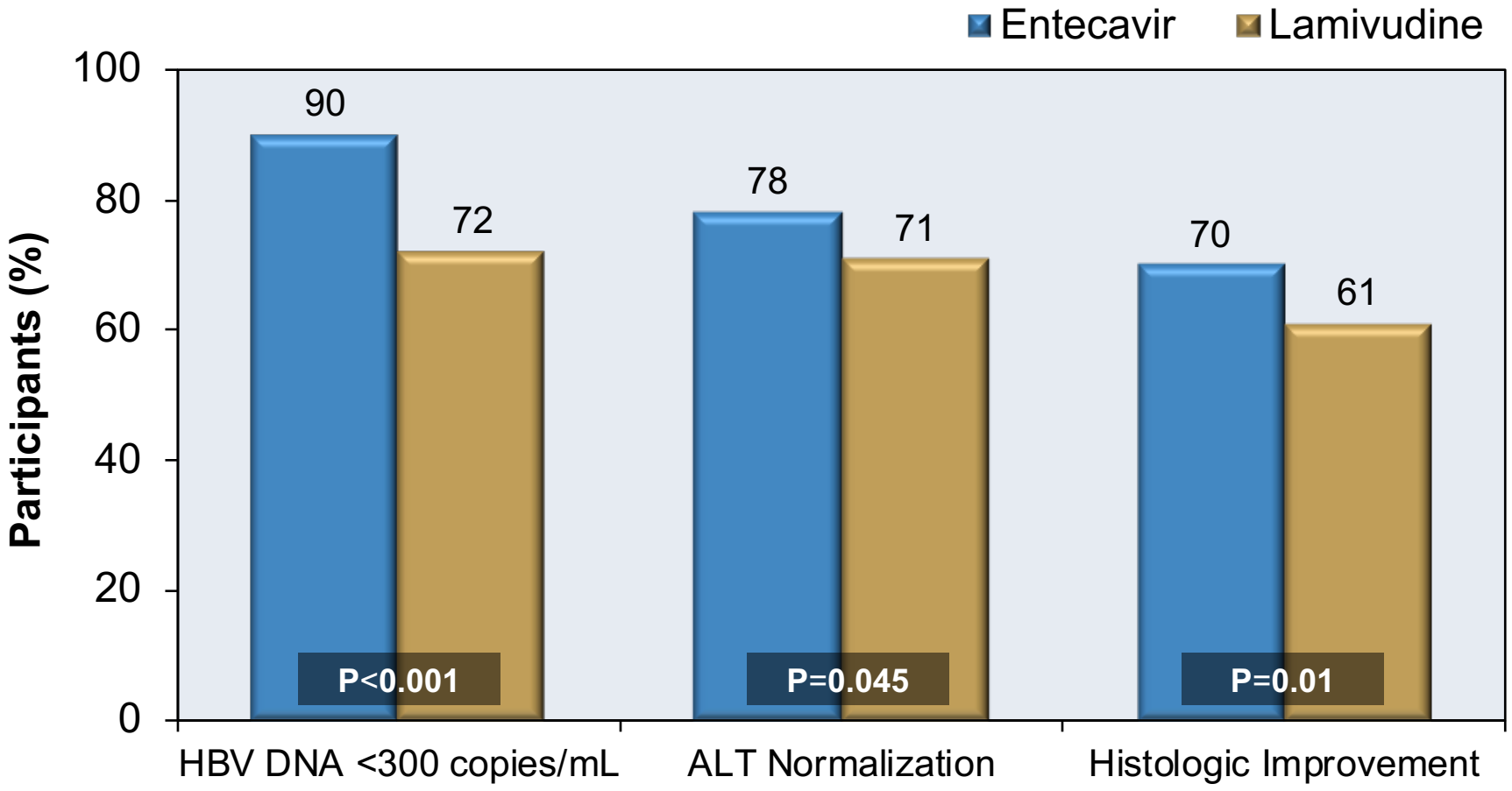
Source: Lai C, et. al. N Engl J Med. 2006;354:1011-21.

Entecavir versus Lamivudine in HBeAg-Negative
BEHoLD (HBeAg-Negative): Baseline Characteristics

Baseline Characteristic	Entecavir (n = 325)	Lamivudine (n = 313)
Age, mean (±SD), years	44 ±11	44 ±11
Male, no. (%)	248 (76)	236 (75)
Race, no. (%)		
White	193 (59)	176 (56)
Asian	122 (38)	129 (41)
Black	8 (2)	7 (2)
Other	2 (<1)	1 (<1)
Knodell inflammatory score, mean (±SD)	7.6 ±1.8	7.6 ±1.7
Ishak fibrosis score, %		
≥3 (bridging fibrosis)	43	41
≥4 (cirrhosis)	5	10
Alanine aminotransferase, IU/mL (±SD)	141 ±114.7	143 ±119.4
Prior treatment w/ interferon or lamivudine, no. (%)	49 (15)	45 (14)

Source: Lai C, et. al. N Engl J Med. 2006;354:1011-21.

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Negative): Results



Source: Lai C, et. al. N Engl J Med. 2006;354:1011-21.

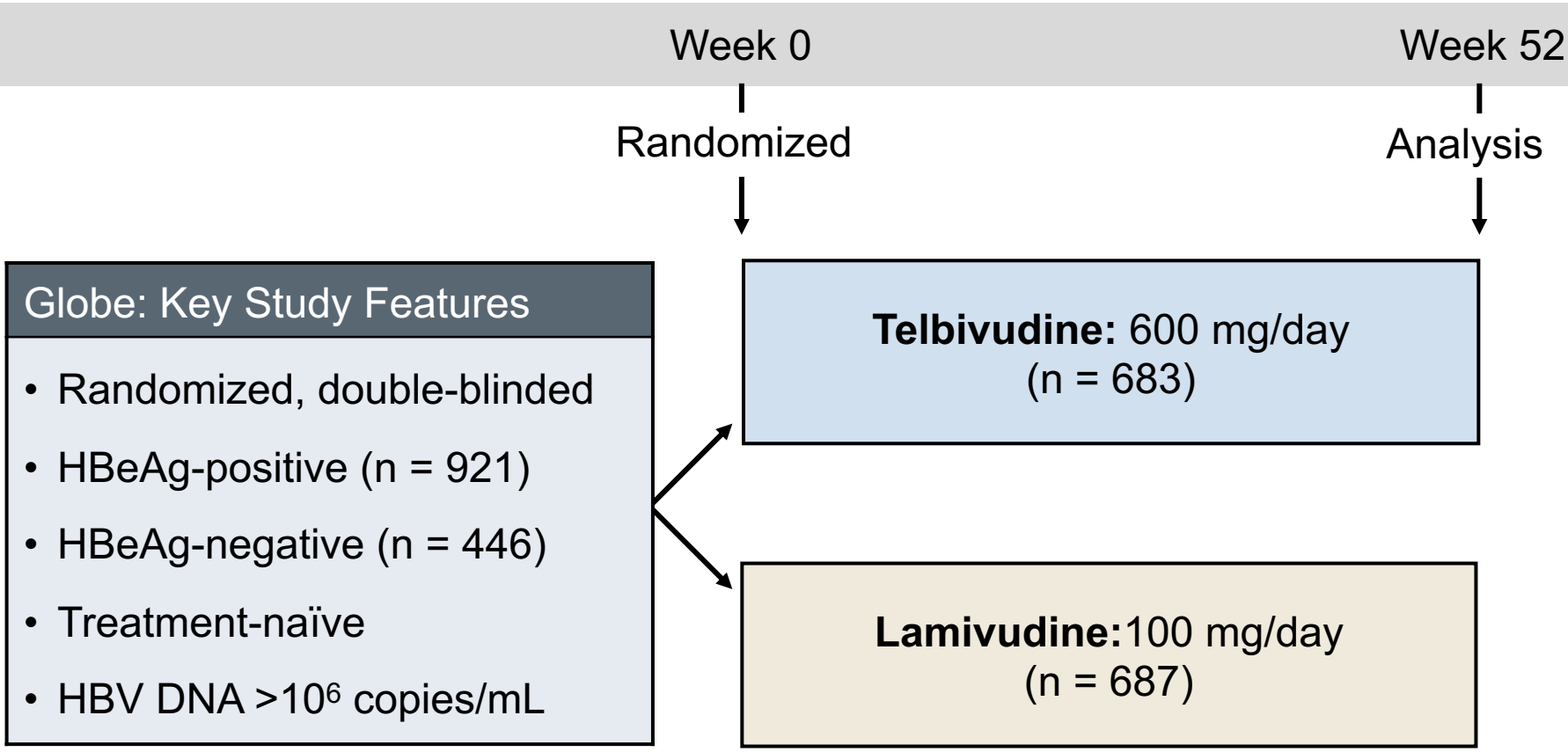
Entecavir versus Lamivudine: 48 Week Data BEHoLD (HBeAg-Negative): Conclusions

Conclusions: “Among patients with HBeAg-negative chronic hepatitis B who had not previously been treated with a nucleoside analogue, the rates of histologic improvement, virologic response, and normalization of alanine aminotransferase levels were significantly higher at 48 weeks with entecavir than with lamivudine. The safety profile of the two agents was similar, and there was no evidence of viral resistance to entecavir.”

Source: Lai C, et. al. N Engl J Med. 2006;354:1011-21.

Telbivudine versus Lamivudine
Globe Study: 52 Weeks

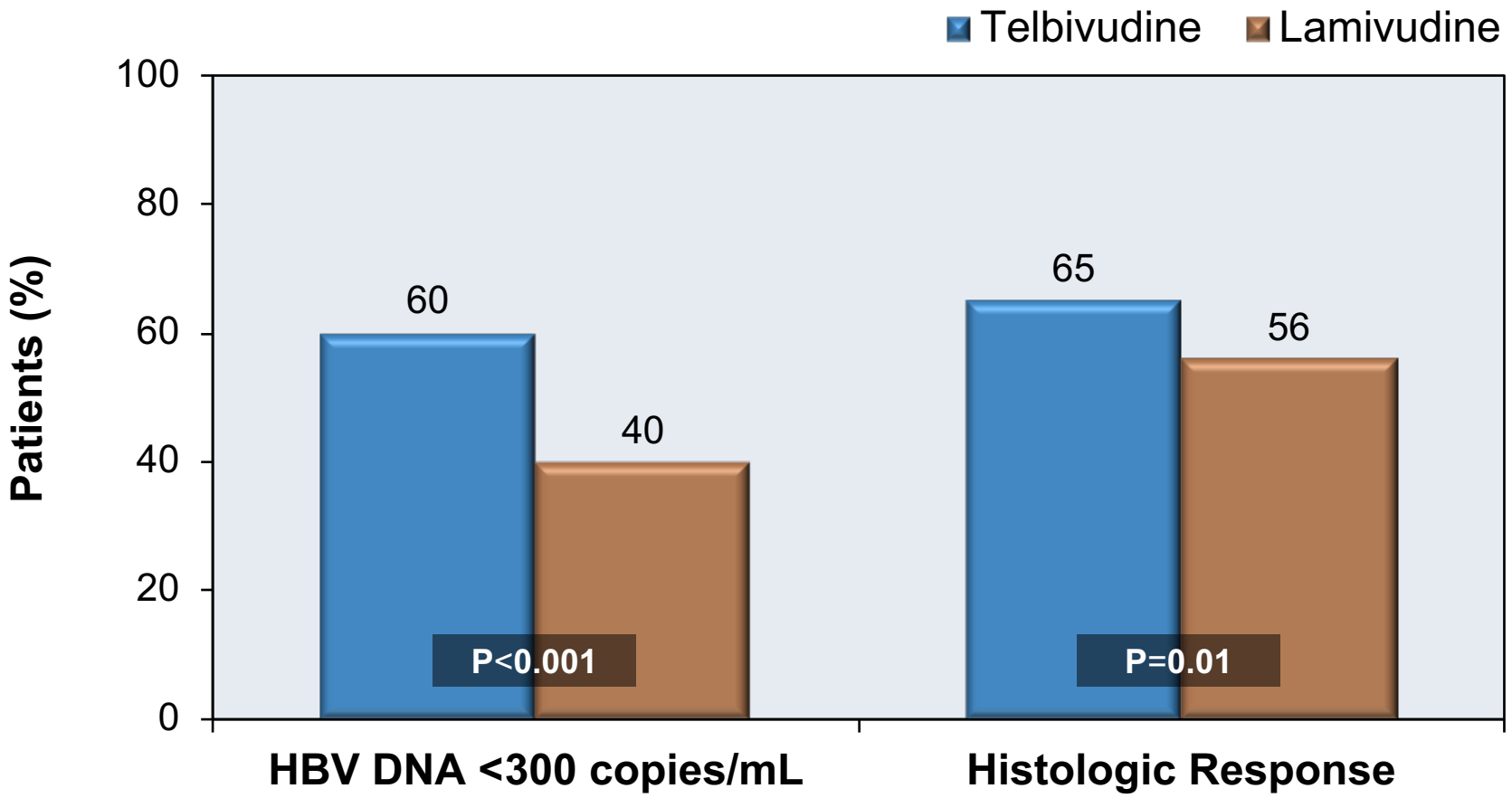
Telbivudine versus Lamivudine Globe Study: Design



Source: Lai CL, et. al. N Engl J Med. 2007;357:2576-88.

Telbivudine versus Lamivudine Globe Study: Results

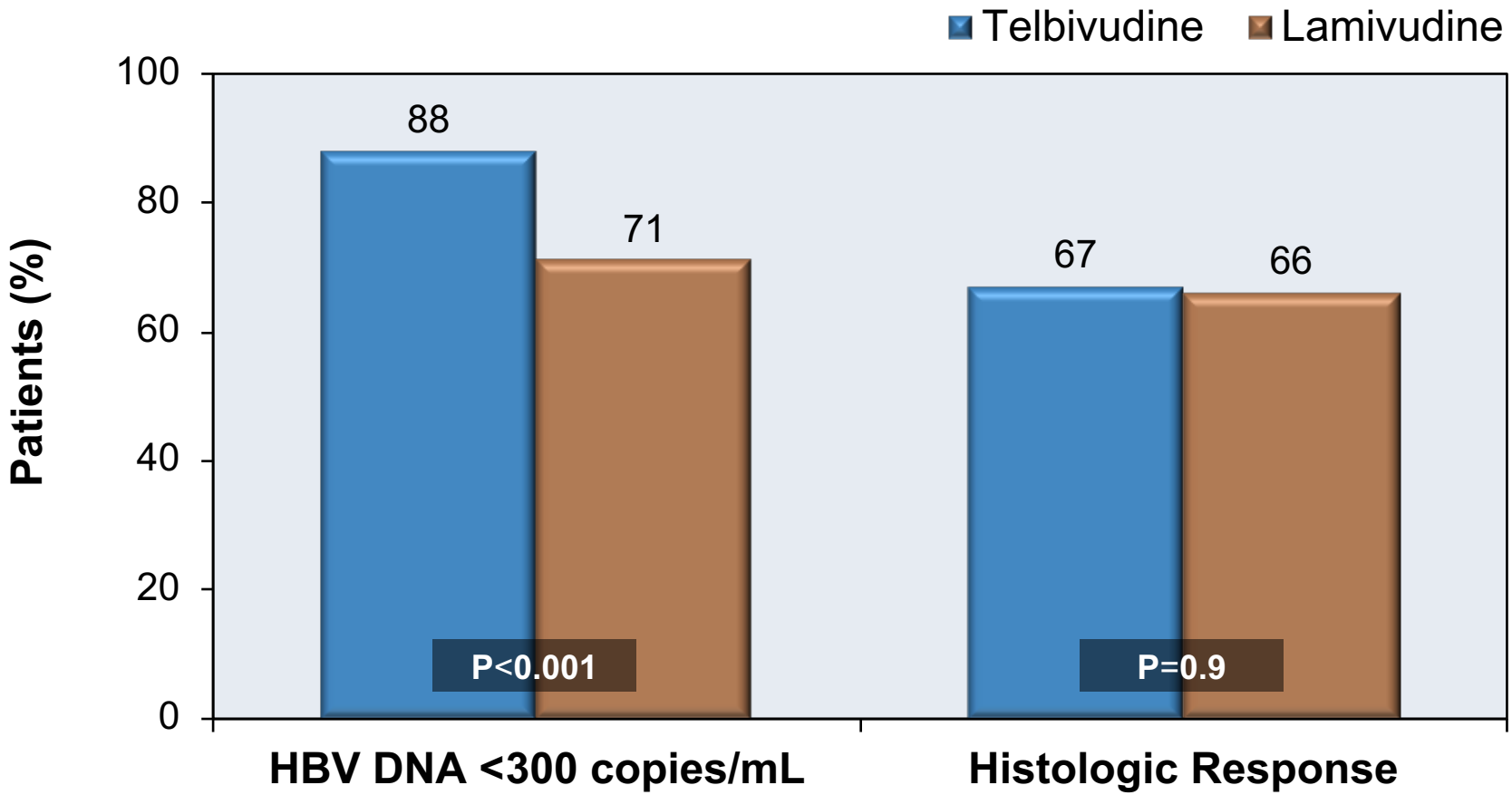
HBeAg-POSITIVE Patients: Week 52 Treatment Response



Source: Lai CL, et al. N Engl J Med. 2007;357:2576-88.

Telbivudine versus Lamivudine Globe Study: Results

HBeAg-NEGATIVE Patients: Week 52 Treatment Response



Source: Lai CL, et al. N Engl J Med. 2007;357:2576-88.

Telbivudine versus Lamivudine Globe Study: Conclusions

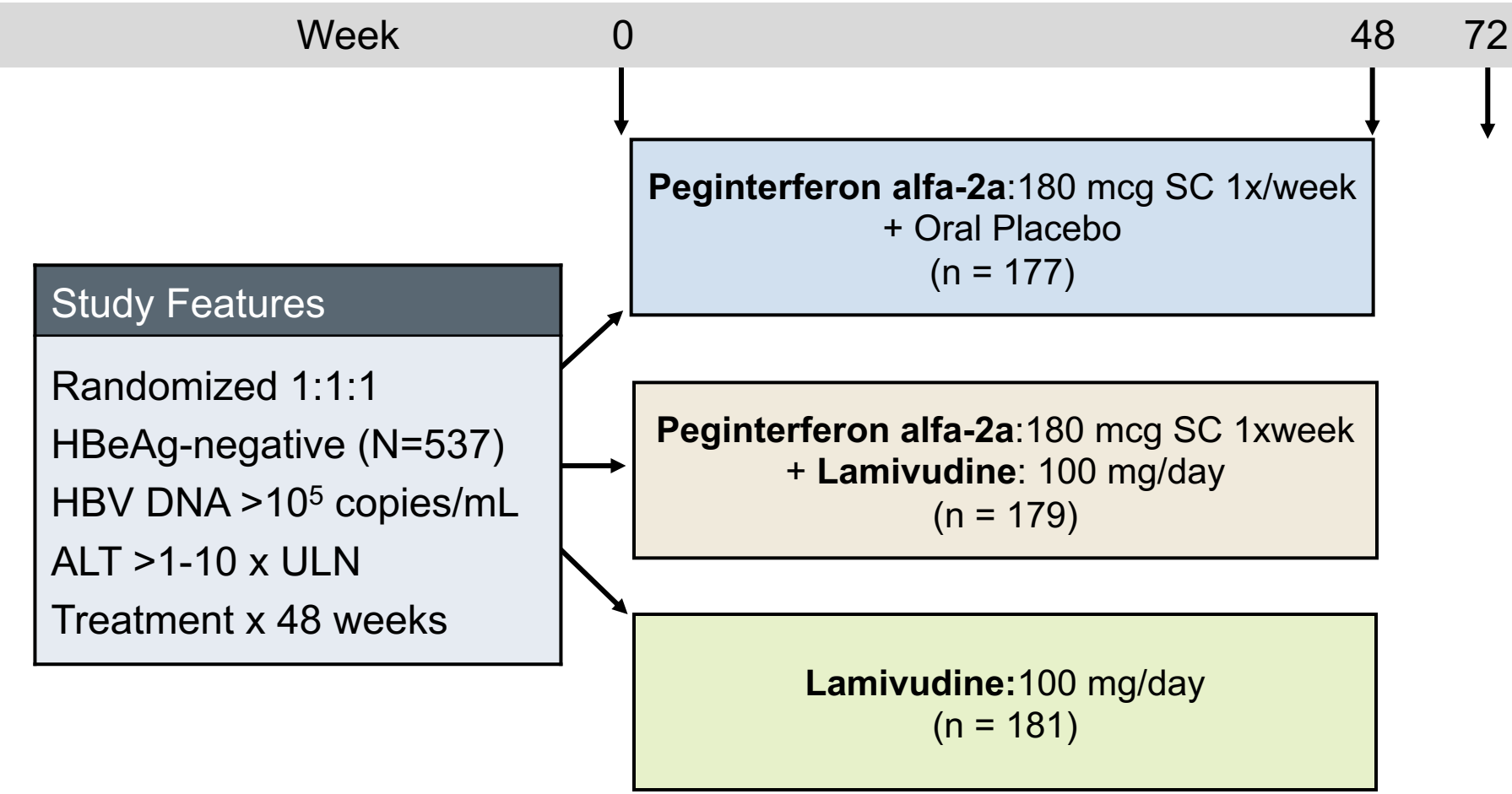
Conclusions: “Among patients with HBeAg-positive chronic hepatitis B, the rates of therapeutic and histologic response at 1 year were significantly higher in patients treated with telbivudine than in patients treated with lamivudine. In both the HBeAg-negative and the HBeAg-positive groups, telbivudine demonstrated greater HBV DNA suppression with less resistance than did lamivudine.”

Source: Lai CL, et al. N Engl J Med. 2007;357:2576-88.

HBeAg-Negative

PegINF alfa-2a versus Lamivudine versus Both

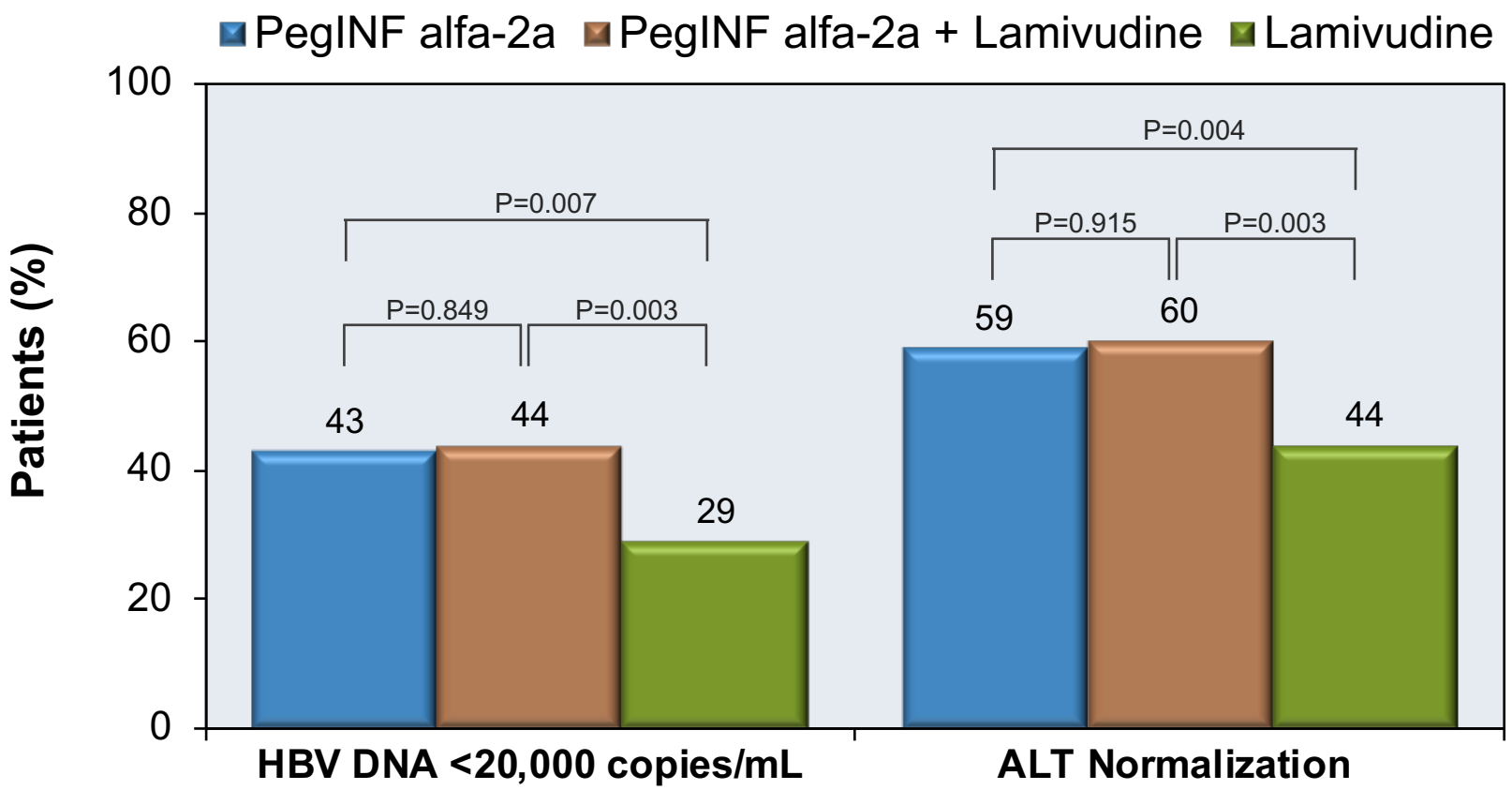
PegINF alfa-2a versus Lamivudine versus Both HBeAg-Negative Patients: Study Design



Source: Marcellin P, et al. N Engl J Med. 2004;351:1206-17.

PegINF alfa-2a versus Lamivudine versus Both HBeAg-Negative Patients: Results

HBeAg-NEGATIVE Patients: Week 72 Treatment Response



Source: Marcellin P, et al. N Engl J Med. 2004;351:1206-17.

PegINF alfa-2a versus Lamivudine versus Both HBeAg-Negative Patients: Conclusions

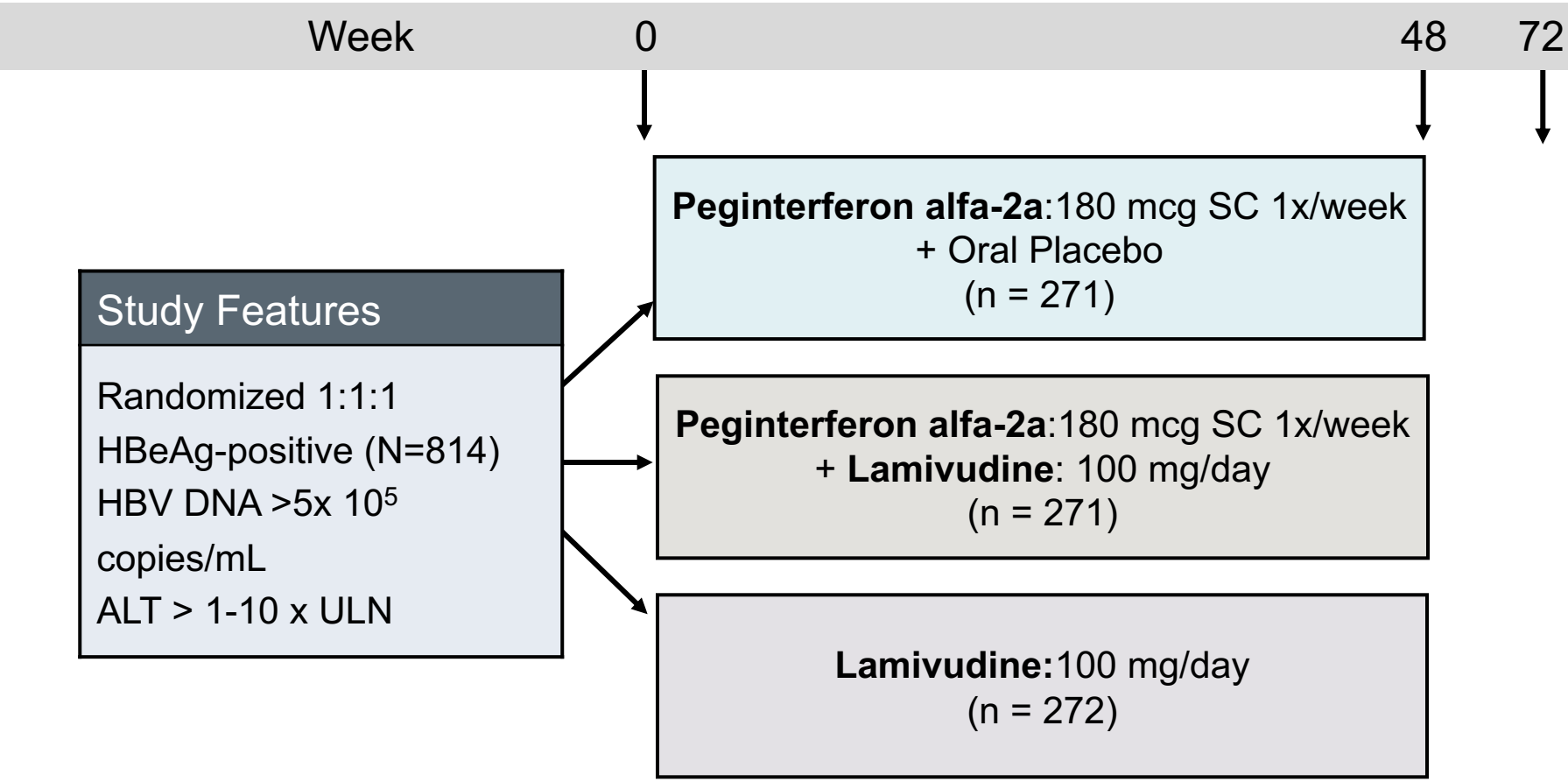
Conclusions: “Patients with HBeAg-negative chronic hepatitis B had significantly higher rates of response, sustained for 24 weeks after the cessation of therapy, with peginterferon alfa-2a than with lamivudine. The addition of lamivudine to peginterferon alfa-2a did not improve post-therapy response rates.”

Source: Marcellin P, et al. N Engl J Med. 2004;351:1206-17.

HBeAg-Positve

PegINF alfa-2a versus Lamivudine versus Both

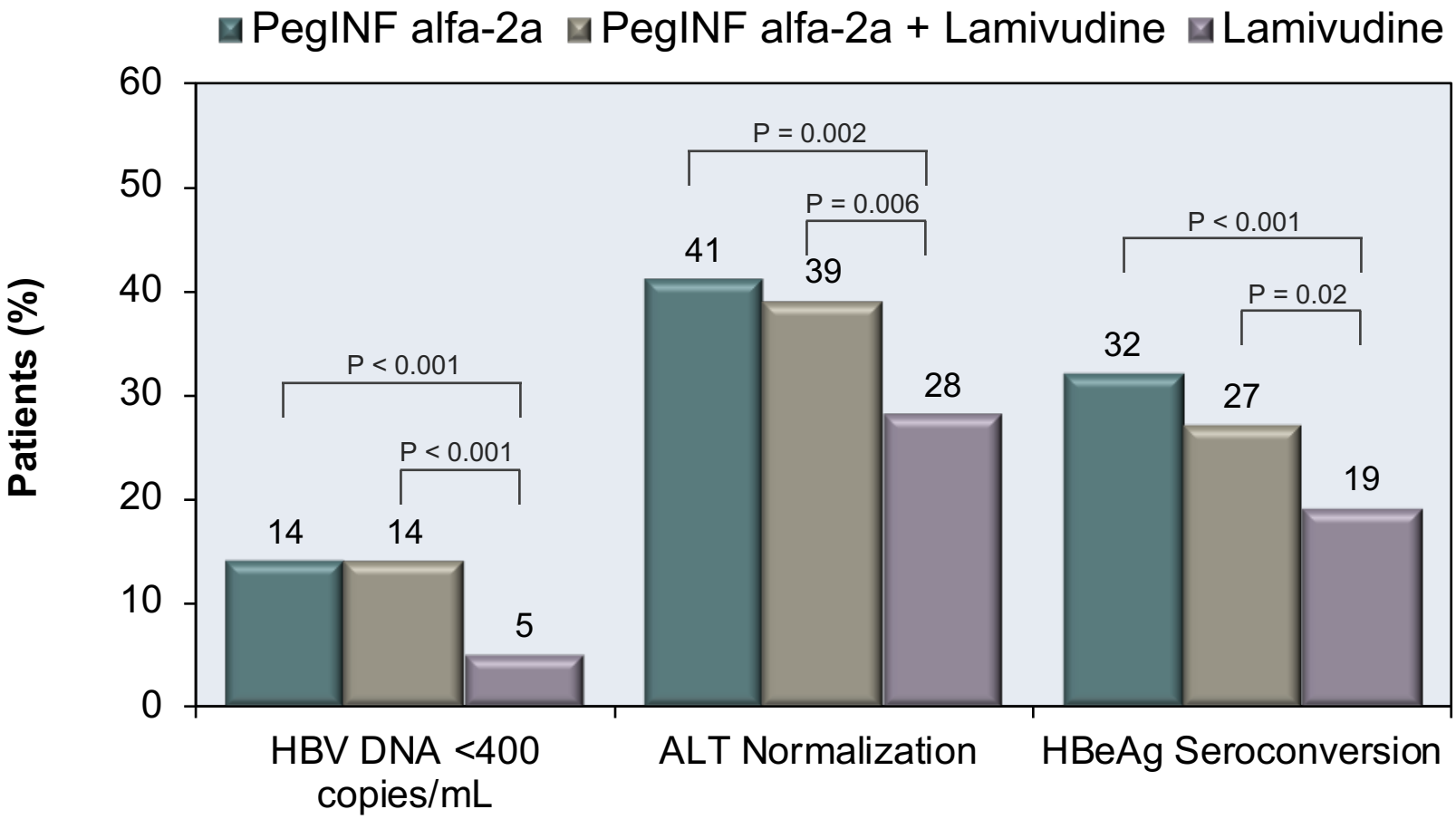
PegINF alfa-2a versus Lamivudine versus Both HBeAg-Positive Patients: Study Design



Source: Lau GK, et al. N Engl J Med. 2005;352:2682-95.

PegINF alfa-2a versus Lamivudine versus Both HBeAg-Positive Patients: Results

HBeAg-Positive Patients: Week 72 Treatment Response



Source: Lau GK, et al. N Engl J Med. 2005;352:2682-95.

PegINF alfa-2a versus Lamivudine versus Both HBeAg-Positive Patients: Conclusions

Conclusions: “In patients with HBeAg-positive chronic hepatitis B, peginterferon alfa-2a offers superior efficacy over lamivudine, on the basis of HBeAg seroconversion, HBV DNA suppression, and HBsAg seroconversion.”

Source: Lau GK, et al. N Engl J Med. 2005;352:2682-95.

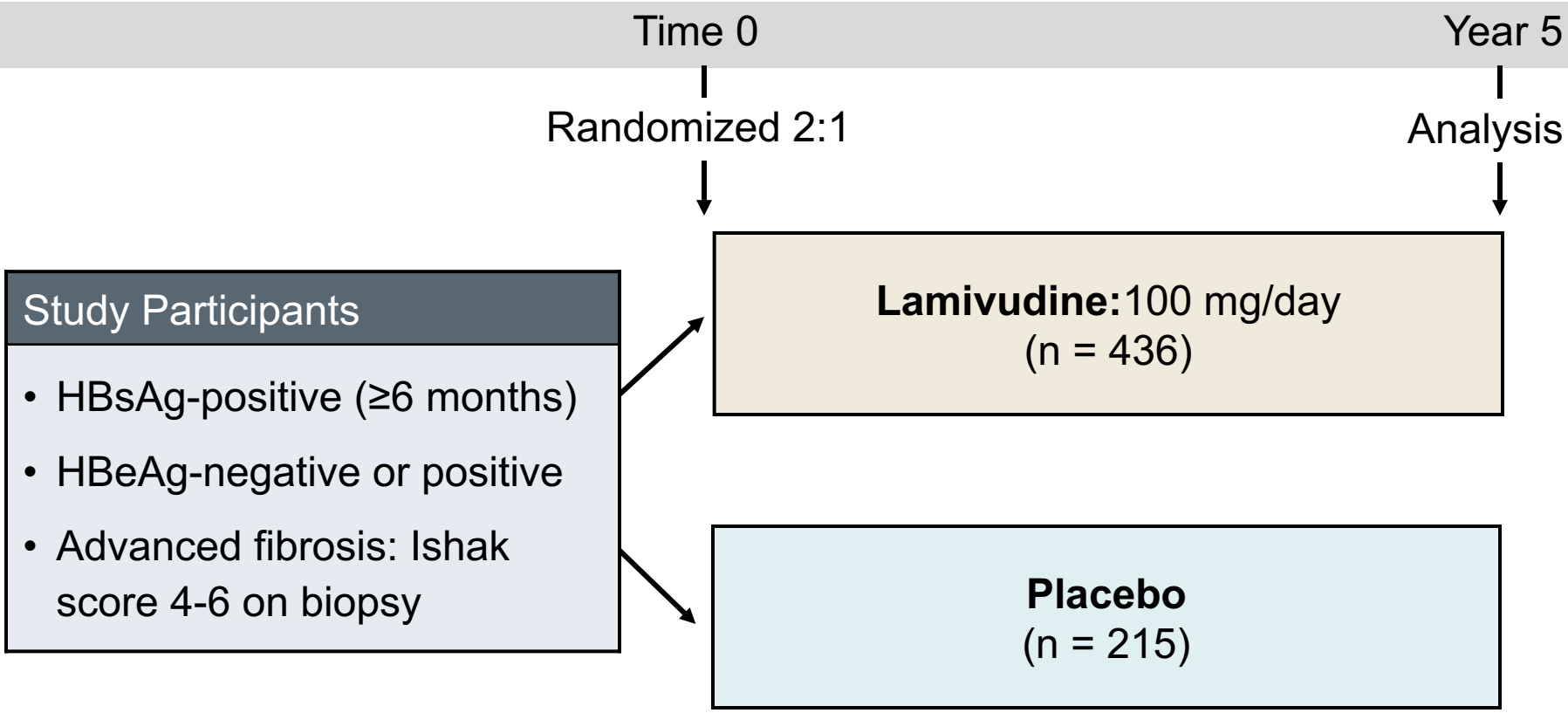
Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease

Lamivudine for Chronic HBV & Advanced Fibrosis Study Design

- **Background**
  - Randomized double-blind placebo-controlled trial of lamivudine in patients with advanced fibrosis to assess efficacy in impacting liver disease progression
- **Subjects**
  - N = 651 with chronic HBeAg-negative or HBeAg-positive
  - All had advanced fibrosis = Ishak fibrosis score of 4-6.
- **Regimen**
  - Lamivudine 100 mg once daily versus placebo
- **Study End-Point**
  - Disease progression (any one of following): ≥2-point increase in Child Pugh score; spontaneous bacterial peritonitis; renal insufficiency (decline in CrCl <50); bleeding varices; HCC; death related to liver disease

Source: Liaw et. al. N Engl J Med. 2004;351:1521-31.

Lamivudine for Chronic HBV & Advanced Fibrosis Study Design



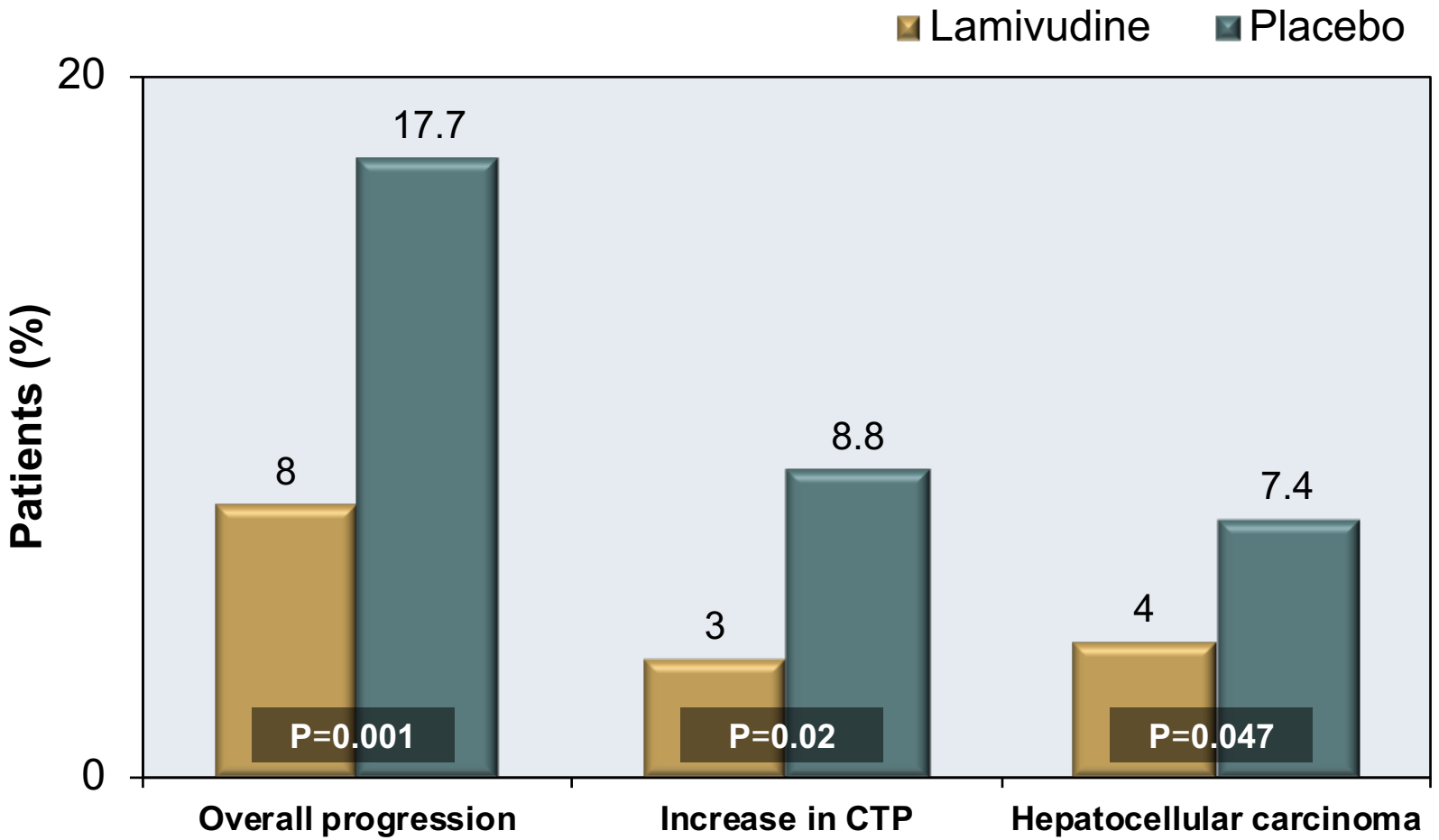
Source: Liaw et. al. N Engl J Med. 2004;351:1521-31.

Lamivudine for Chronic HBV & Advanced Fibrosis Baseline Characteristics

Baseline Characteristic	Lamivudine (n = 436)	Placebo (n = 215)
Age, median (range), years	43 (17-74)	44 (22-71)
Male, n (%)	370 (85)	182 (85)
Asian, n (%)	426 (98)	210 (98)
HBeAg positive, n (%)	252 (58)	124 (58)
Child-Pugh score, n (%)		
5	341 (78)	156 (73)
6	75 (17)	41 (19)
≥7	20 (5)	18 (8)
Ishak fibrosis score, n (%)		
4	176 (40)	76 (35)
5	127 (29)	55 (26)
6	133 (31)	84 (39)
Median HBV DNA, mEq/mL (range)	11.7 (<0.7-109,800)	21.5 (<0.7-4234)

Source: Liaw et. al. N Engl J Med. 2004;351:1521-31.

Lamivudine for Chronic HBV & Advanced Fibrosis Disease Progression



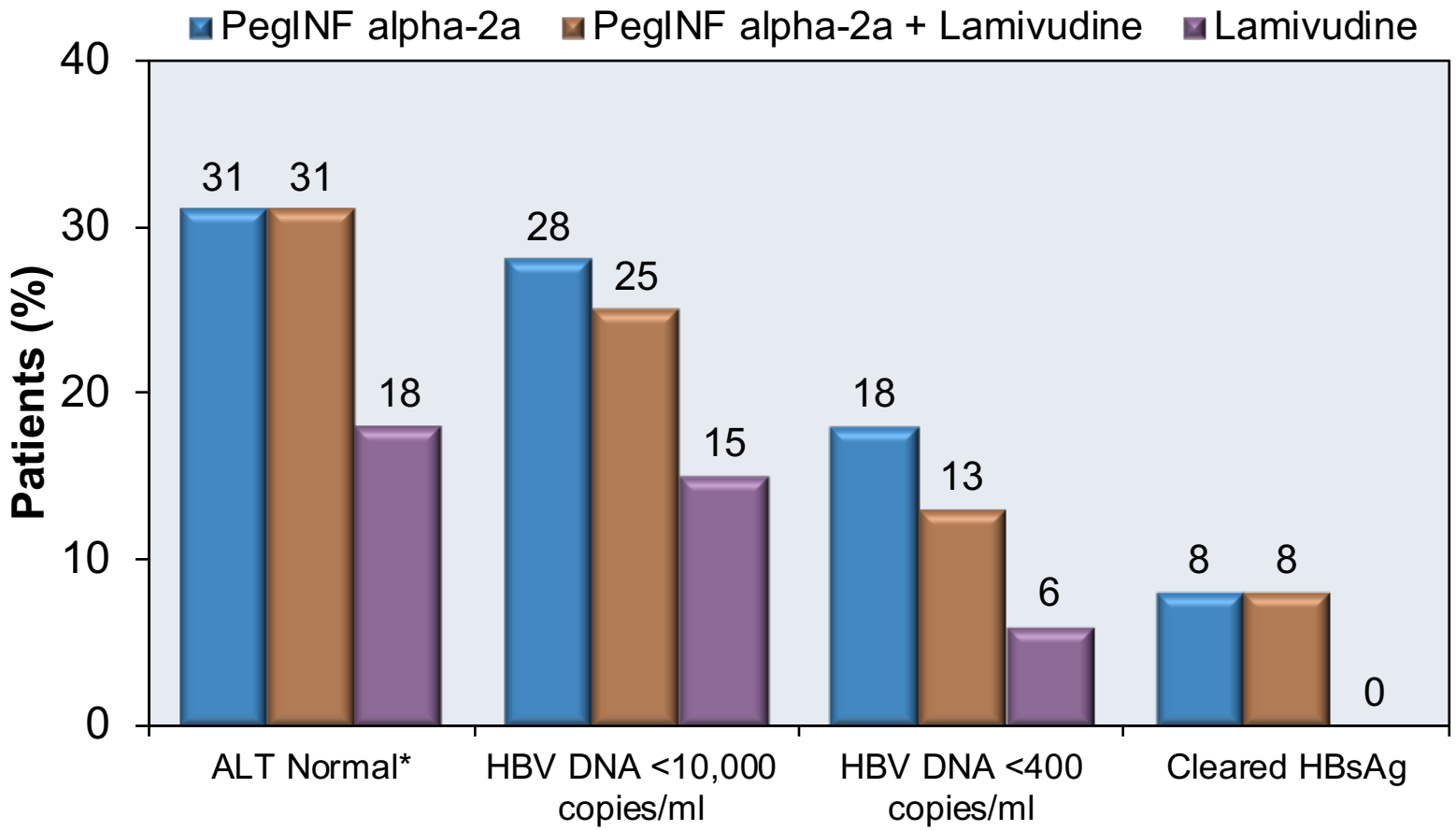
Source: Liaw et. al. N Engl J Med. 2004;351:1521-31.

Lamivudine for Chronic HBV & Advanced Fibrosis Conclusions

Conclusions: “Continuous treatment with lamivudine delays clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of hepatocellular carcinoma.”

Source: Liaw et. al. N Engl J Med. 2004;351:1521-31.

Data 3 Years After Completing 48 Weeks of Therapy



Source: Marcellin P, et al. Gastroenterology. 2009;136:2169-79.

Questions?