Hepatitis B Medications

Entecavir (*Baraclude*)

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Entecavir (ETV)
Summary of Key Studies

- Phase 3 Trials
  - BeHOLD (HBeAg+): ETV versus 3TC in HBeAg-Positive
  - BeHOLD (HBeAg-): ETV versus 3TC in HBeAg-Negative

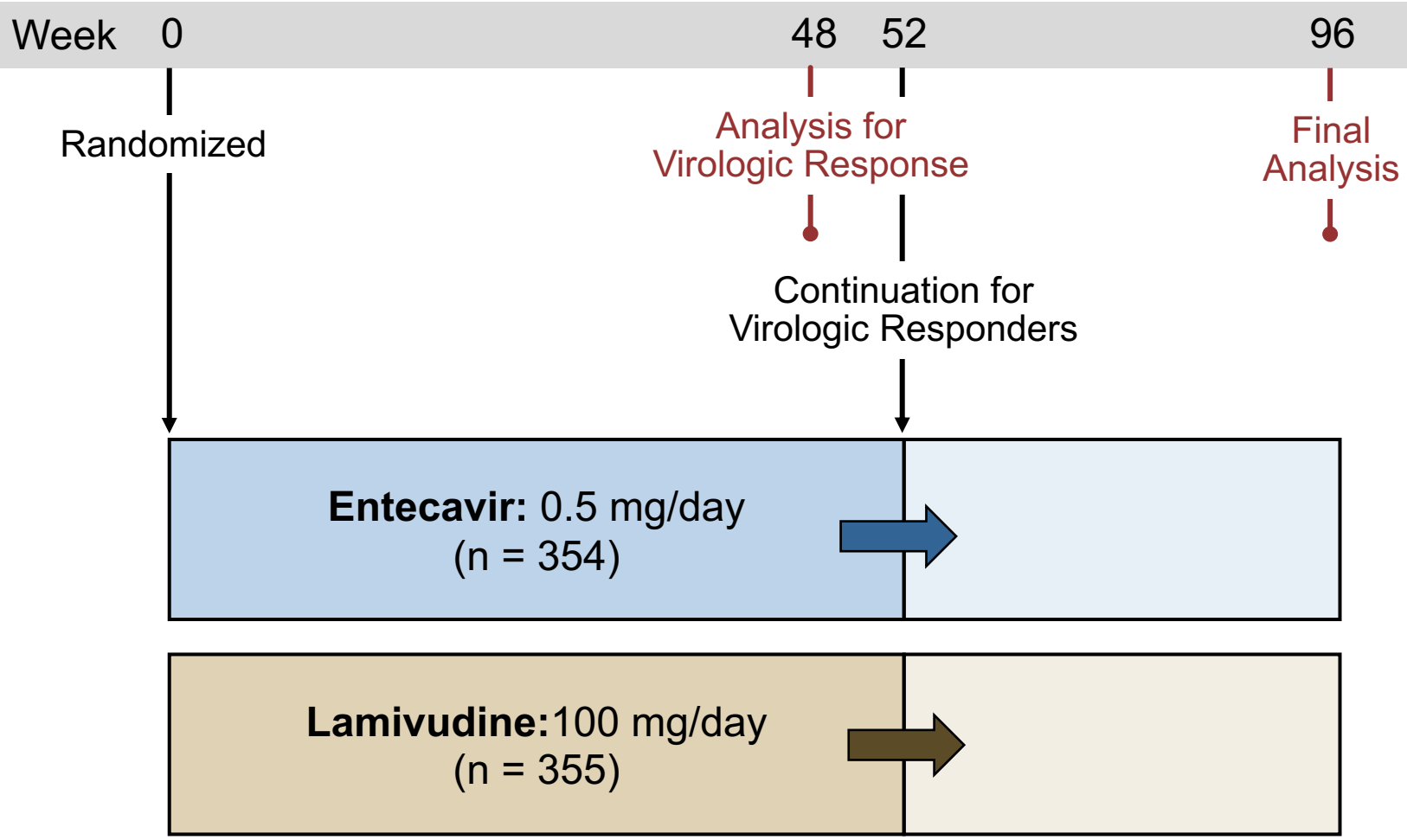
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD: HBeAg-Positive, Week 48

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.

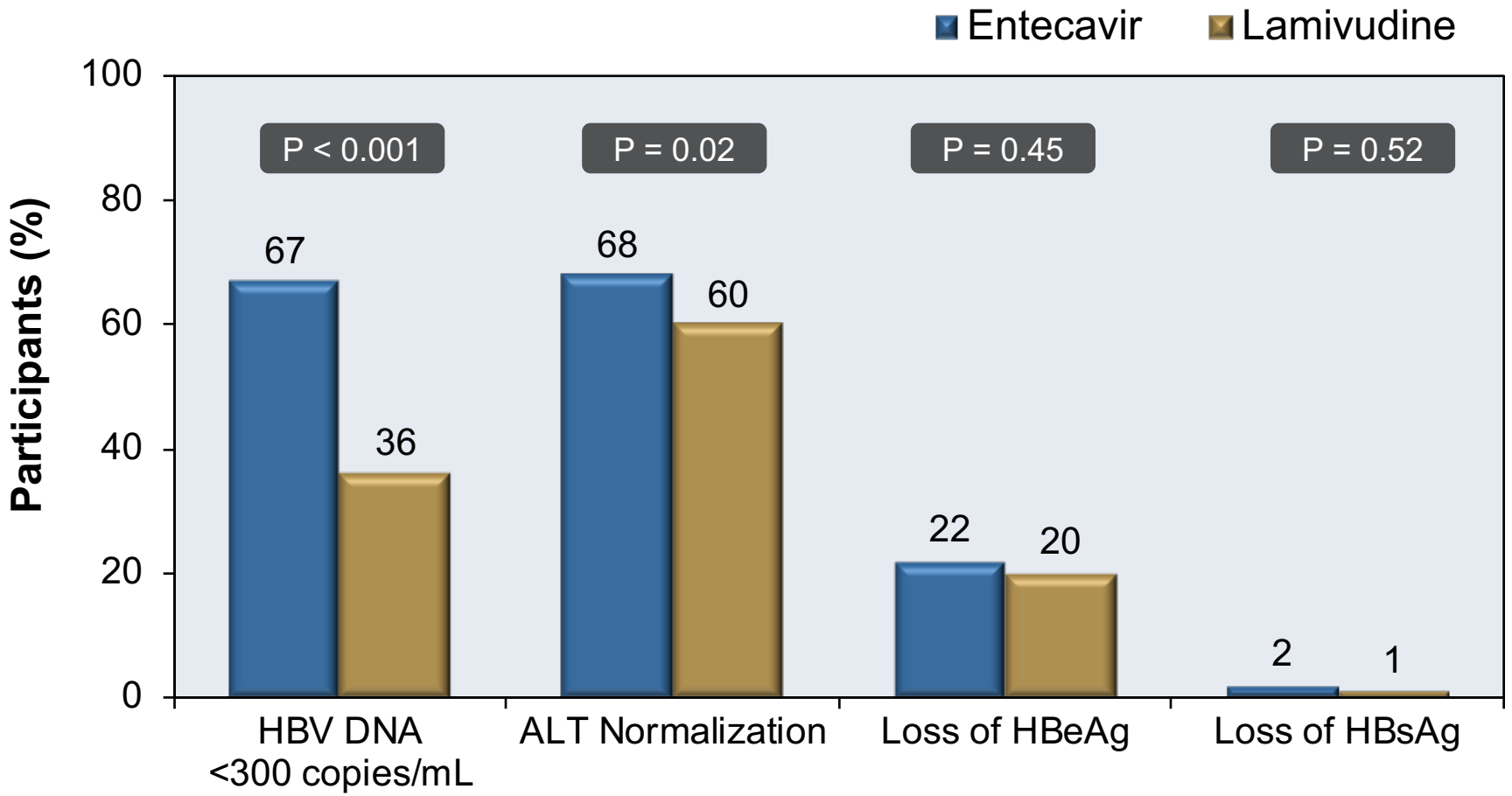
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Positive): Study Design



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.

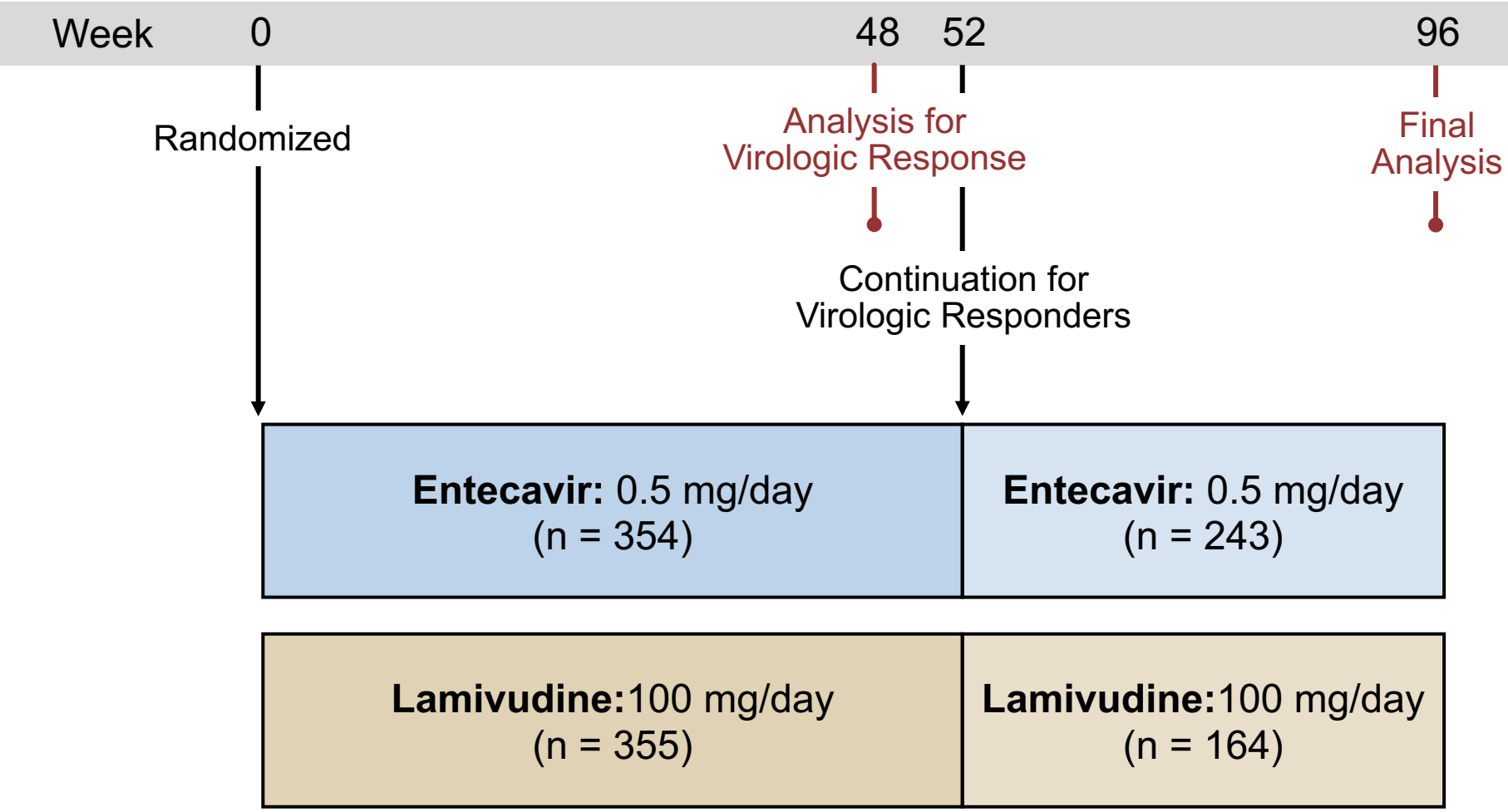
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD: HBeAg-Positive, Week 96

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.

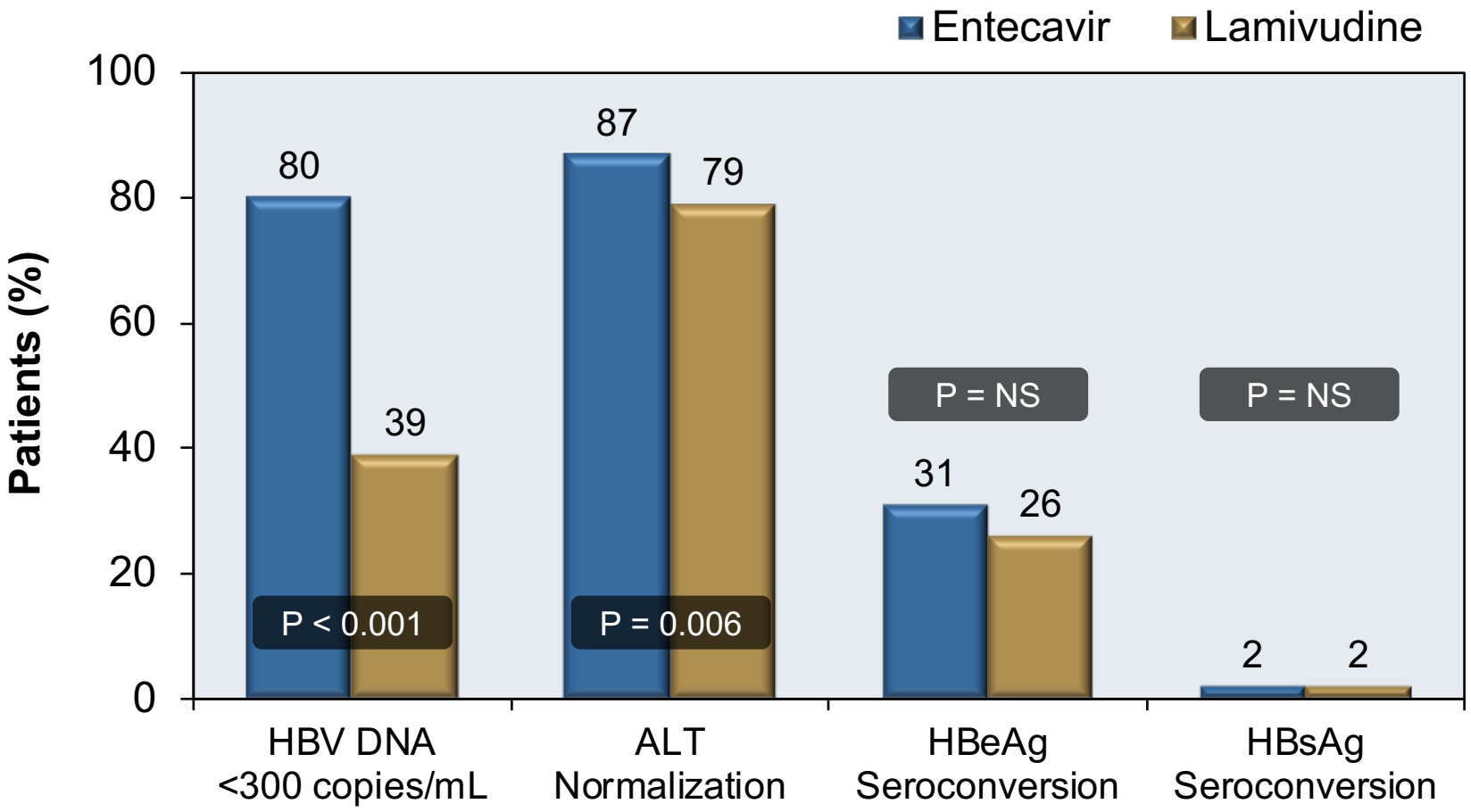
Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Study Design



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

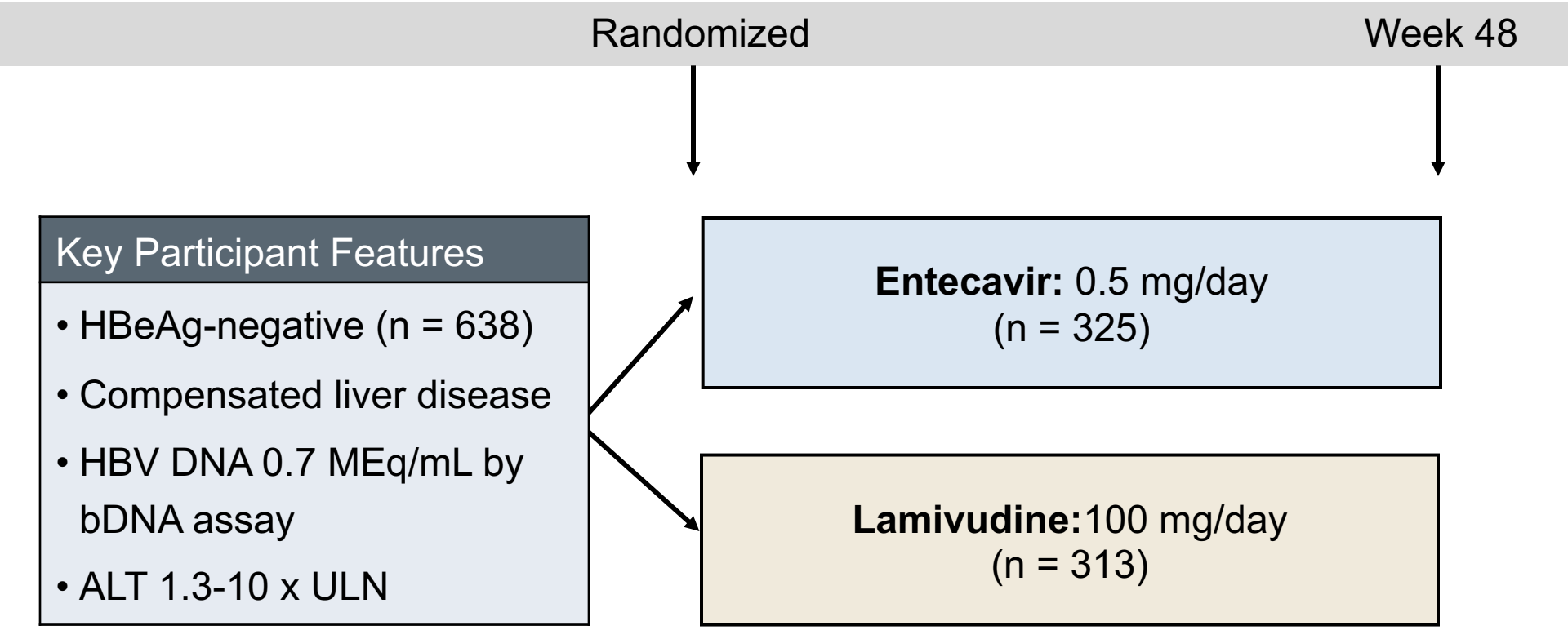
BEHoLD: HBeAg-Negative

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



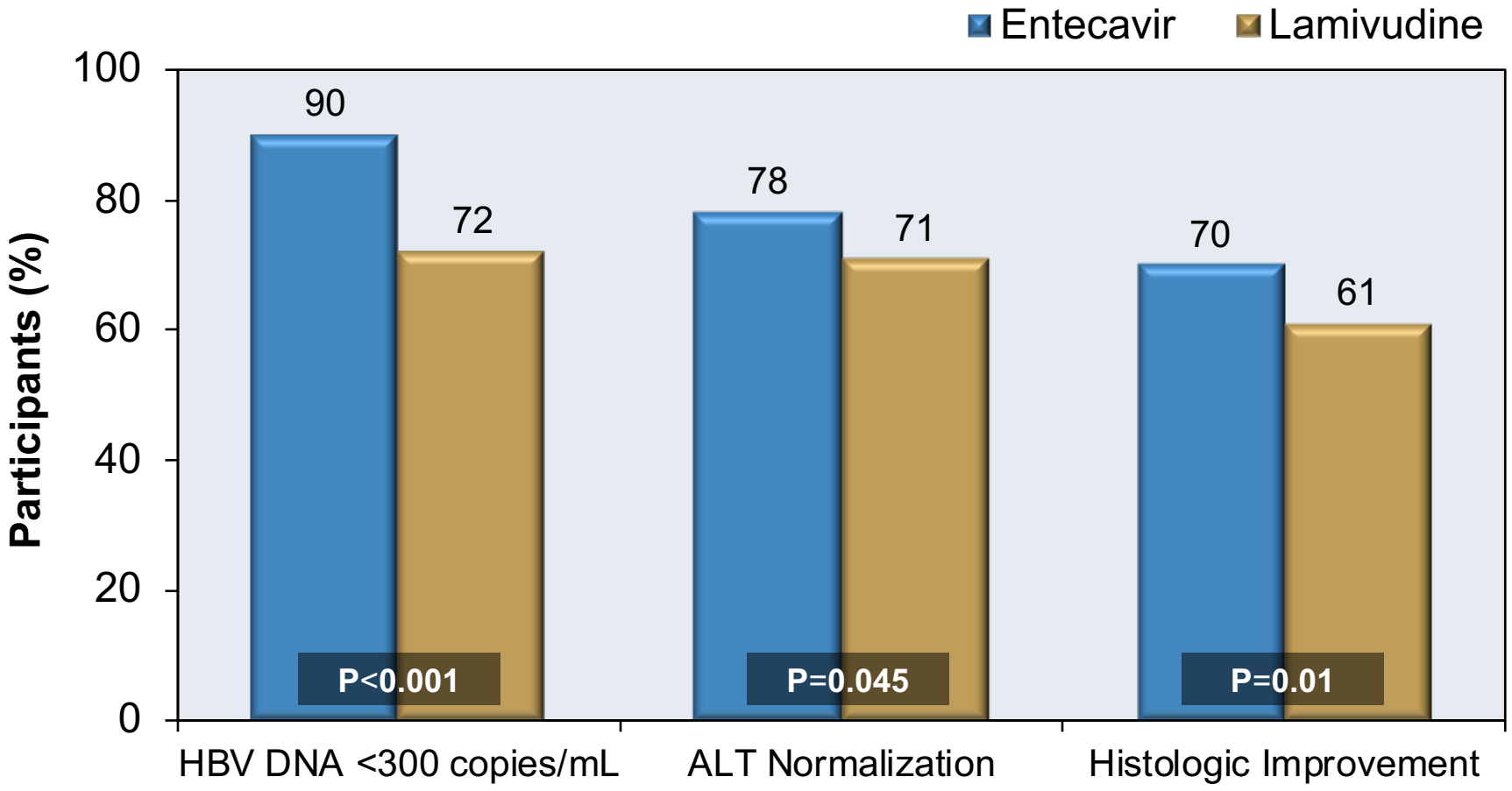
Source: Lai C, et. al. N Engl J Med. 2006;354:1011-21.

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.