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Long-term Entecavir Therapy Results in Reversal of Fibrosis/Cirrhosis and Continued Histologic Improvement in Patients with HBeAg(+) and (-) Chronic Hepatitis B: Results from Studies ETV-022, -027 and -901

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Introduction

- Elevated baseline HBV DNA has been demonstrated to be a significant factor in the development of cirrhosis and hepatocellular carcinoma[1-3]
- HBV DNA suppression with antiviral therapy can significantly improve liver histology in HBeAg(+) patients[4]
- Entecavir (ETV) 0.5 mg daily demonstrated superior histologic, virologic and biochemical activity compared to lamivudine (LVD) 100 mg daily in nucleoside-naïve HBeAg(+) and HBeAg(-) patients with chronic hepatitis B (studies ETV-022 and ETV-027)[5,6]
- We present long-term histologic results for a subset of patients treated with ETV for a median of 280 weeks

Methods

Study population

- The Long-term Histology Cohort (n=69) is a subset of the ETV-901 study population
  - It consists of nucleoside-naïve HBeAg(+) and HBeAg(-) patients treated with ETV in studies ETV-022 or ETV-027 who:
    - had a liver biopsy in study ETV-901 and
    - received a minimum of 3 years of cumulative ETV therapy from Phase 3 baseline to the time of their last observed biopsy in study ETV-901
- Patients received ETV 0.5 mg once daily in studies ETV-022 and -027
- All patients received ETV 1.0 mg in study ETV-901
  - Initially, due to ongoing blinding of Phase 2-3 studies, patients enrolling into study ETV-901 may have received a brief period of combination ETV 1.0 mg and LVD 100 mg daily

Efficacy Evaluable Cohort

- The Efficacy Evaluable Cohort (n=57) consists of patients who had:
  - an adequate Phase 3 baseline biopsy
  - a baseline Knodell necroinflammatory score of ≥2
  - an adequate long-term biopsy sample in study ETV-901

Analysis endpoints: liver histology

- Co-primary endpoints
  - Histologic improvement (≥2-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score) compared to baseline
  - Improvement in Ishak fibrosis score (≥1-point decrease) compared with baseline
- Other histologic endpoints
  - Change from baseline in Knodell necroinflammatory score
  - Change from baseline in Ishak fibrosis score
  - Proportion of patients with baseline advanced fibrosis/cirrhosis (Ishak score ≥4) who demonstrated Ishak score improvement
  - Proportion of subjects with baseline histologic activity index (HAI) score of ≥4 who achieved a Knodell HAI score ≤3

Analysis endpoints: virologic, biochemical, serologic and safety

- All efficacy analyses were conducted on samples that matched the time of long-term biopsy (±12 weeks) and compared with Phase 3 baseline
- Proportions of patients with HBV DNA <300 copies/mL by PCR, alanine aminotransferase (ALT) ≤1 x ULN, HBeAg loss, HBe seroconversion and HBsAg loss were assessed among patients with available samples (Non-completer=Missing)
- Safety was evaluated from entry in study ETV-901 to date of database lock (28 April 2008)

Results

Table 1: Demographics and Baseline Characteristics of Patients in Phase 3 Studies Compared with Efficacy Evaluable Cohort (ETV-901)

	ETV-022 Cohort (n=354)	ETV-027 Cohort (n=325)	Efficacy Evaluable Cohort (n=57)
Age, mean (years)	35	44	40
Male (%)	77	76	82
Race:			
Asian (%)	58	38	67
Non-Asian (%)	42	62	33
HBeAg(+) (%)	98	1	72
HBV DNA by PCR, mean (log_{10} copies/mL)	9.62	7.60	9.40
ALT, mean (U/L)	140	141	142
HBV genotype (%)			
A	13	10	12
B	27	10	18
C	10	14	13
D	31	18	27
Other	19	48	33

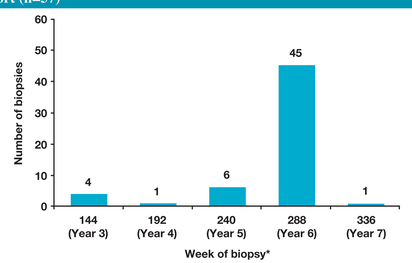
- Demographics and baseline characteristics of the Efficacy Evaluable Cohort were generally comparable to those of all treated patients in studies ETV-022 and -027, with the exception of the higher proportion of Asians in the Efficacy Evaluable Cohort

Table 2: Comparison of Results Between Efficacy Evaluable Cohort and ETV-022 and ETV-027 at Week 48

	HBeAg(+) patients		HBeAg(-) patients	
	Efficacy Evaluable Cohort (n=41)	ETV-022 (n=354)	Efficacy Evaluable Cohort (n=16)	ETV-027 (n=325)
HBV DNA <300 copies/mL, n (%)	25 (61)	236 (67)	15 (94)	293 (90)
ALT <1 x ULN, n (%)	26 (63)	242 (68)	12 (75)	253 (78)
Histologic improvement,* n (%)	31 (76)	226 (77)†	10 (67)‡	202 (78)§
Improvement in Ishak fibrosis score, n (%)±	15 (37)	121 (41)†	3 (20)‡	107 (40)§

* ≥2-point decrease in Knodell HAI score and no worsening of Knodell fibrosis score compared with baseline
† A total of 292 patients had adequate paired biopsy samples
‡ One patient had an inadequate Week 48 biopsy
§ A total of 265 patients had adequate paired biopsy samples
± ≥1-point decrease in Ishak fibrosis score

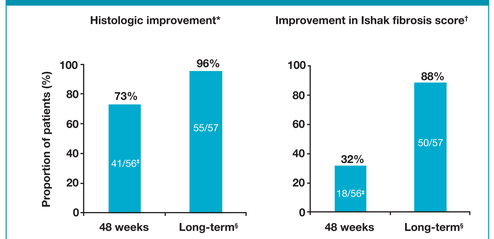
Figure 1: Distribution of Biopsies Included in the Efficacy Evaluable Cohort (n=57)



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

- Median time on treatment at the time of long-term biopsy was 280 weeks

Figure 2: Analysis Endpoints: Liver Histology



* ≥ 2-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score compared with baseline
† ≥1-point decrease
‡ One patient had an inadequate Week 48 biopsy
§ Median time of long-term biopsy = 280 weeks (range: 144–316 weeks)

- Following 48 Weeks of ETV treatment the majority (73%) of patients achieved histologic improvement
  - The proportion of patients who achieved histologic improvement increased to 96% following long-term treatment
- Improvement in Ishak Fibrosis score was observed in 32% of patients following 48 Weeks of ETV treatment
  - This increased to 88% following long-term treatment

Figure 3: Distribution of Knodell Necroinflammatory Scores at Baseline, Year 1, and Years 3–7

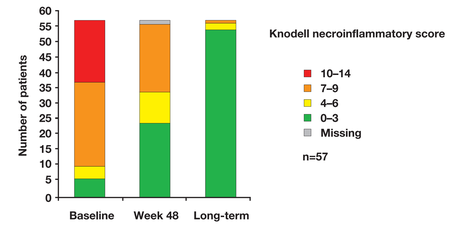


Figure 4: Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Years 3–7

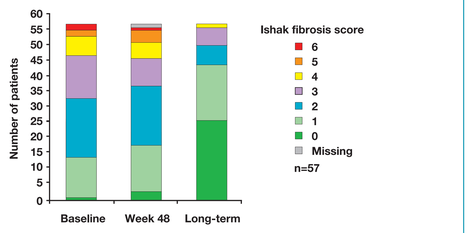


Table 3: Change in Knodell Necroinflammatory Score and HAI from Baseline

	Efficacy Evaluable Cohort (n=57)	
	Week 48	Long-term*
Mean change from baseline in Knodell necroinflammatory score	-3.39	-6.37
Knodell HAI <3 in patients with baseline HAI ≥4, n (%)†	12/54 (22)‡	41/55 (75)

* Median time of long-term biopsy: 280 weeks (range: 144–316 weeks);
† Fifty-five patients had baseline Knodell HAI score ≥4
‡ One patient had an inadequate Week 48 biopsy

Table 4: Change in Ishak Fibrosis Score from Baseline

	Efficacy Evaluable Cohort (n=57)	
	Week 48	Long-term*
Mean change from baseline in Ishak fibrosis score	-0.20	-1.53
≥2-point decrease in Ishak fibrosis score, n (%)†	3/42 (7)‡	25/43 (58)

* Median time of long-term biopsy: 280 weeks (range: 144–316 weeks);
† Forty-three patients had baseline Ishak fibrosis score ≥2
‡ One patient had an inadequate Week 48 biopsy

Table 5: Analysis Endpoints: Virologic, Biochemical and Serologic

	Efficacy Evaluable Cohort (n=57)	
	Week 48	Long-term*
HBV DNA <300 copies/mL, n (%)	40/57 (70)	57/57 (100)
ALT ≤1 x ULN, n (%)	38/57 (67)	49/57 (86)
HBeAg loss, n (%)†	1/41 (2)	22/40 (55)‡
HBe seroconversion, n (%)†	1/41 (2)	13/40 (33)‡

* Median time of long-term biopsy: 280 weeks (range: 144–316 weeks)
† Only HBeAg(+) patients (n=41)
‡ One patient with missing serology in long-term window

- All patients achieved undetectable HBV DNA (<300 copies/mL) at the time of long-term biopsy
- Increasing proportions of patients achieved ALT normalization (ALT <1 x ULN) with long-term ETV treatment
- Patient management criteria in ETV-022 mandated that patients with HBeAg loss and HBV DNA <0.7 MEq/mL discontinue study therapy and be followed off-treatment. Most patients who achieved HBeAg loss in ETV-022 were therefore not included in the Long-term Histology Cohort
- No patients in the Evaluable Efficacy Cohort lost HBsAg

Table 6: Cumulative Safety of Patients in the Long-term Histology Cohort During Treatment in ETV-901 (n=69)*

	n (%)
Any adverse event	66 (96)†
Grade 3–4 adverse events	14 (20)
Serious adverse events	17 (25)
Discontinuation due to adverse event	0 (0)
All deaths	1 (1)‡
On-treatment ALT flares±	2 (3)

* Safety was evaluated from entry in Study ETV-901 to date of data base lock (04/28/08); † Most common adverse events, occurring in ≥10% of patients: upper respiratory tract infection (23%), headache (16%), nasopharyngitis (16%), ALT increase (14%), abdominal pain (13%), influenza (13%), back pain (12%), pyrexia (12%), arthralgia (10%), cough (10%), hypertension (10%), insomnia (10%) and pharyngolaryngeal pain (10%); ‡ One death occurred due to myocardial ischemia and was not attributed to study medication;
± ALT flare = ALT >2 x baseline ALT and >10 x ULN

Reversal of advanced fibrosis/cirrhosis

- Ten patients had baseline advanced fibrosis/cirrhosis (Ishak fibrosis score = 4, 5 or 6)
  - All demonstrated an improvement in Ishak fibrosis score (≥1-point improvement)
  - Four patients had a liver biopsy with cirrhosis at baseline; all demonstrated an improvement of Ishak fibrosis score
    - The median change in Ishak fibrosis score was a 3-point decrease (range: –1 to –4)

Summary of Results

- Ninety-six percent of patients in the Long-term Histology Cohort who received continuous treatment with ETV achieved histologic improvement
- All patients with advanced fibrosis/cirrhosis at baseline (Ishak fibrosis score ≥4) demonstrated an improvement in fibrosis
- At the time of long-term biopsy:
  - all patients had HBV DNA <300 copies/mL
  - eighty-six percent of patients had ALT <1 x ULN
- Week 48 results for the Efficacy Evaluable Cohort were comparable to the respective Phase 3 parent studies (ETV-022 and ETV-027)
- Safety profile was consistent with previously reported experience

Conclusion

- The results from this cohort demonstrate that long-term ETV treatment result in durable suppression of viral replication and regression of fibrosis/cirrhosis

References

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Disclosures

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