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Regression of Fibrosis/Cirrhosis with Long-Term Entecavir Therapy in Chronic Hepatitis B (CHB) Patients with Baseline Bridging Fibrosis or Cirrhosis: Results from Studies ETV-022, -027 and -901

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Introduction

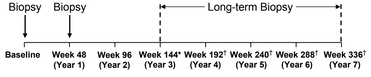
- Elevated HBV DNA is associated with the development of cirrhosis and hepatocellular carcinoma[1,2]
- Treatment with the nucleoside analogue lamivudine (LVD), slowed progression of disease in CHB patients with advanced fibrosis or cirrhosis[3]
- In a subgroup of patients with advanced fibrosis or cirrhosis from studies ETV-022 (HBeAg+) and -027 (HBeAg-), entecavir (ETV) resulted in higher observed virologic, histologic, and biochemical efficacy compared to LVD at 48 weeks[4]
- Results from the ETV long-term histology cohort showed that treatment for a median of 6 years resulted in durable virologic suppression and continued histologic improvement[5]
- We present results for a subset of patients from the long-term histology cohort with the most advanced fibrosis at baseline

Methods

Study population:
A subset of the Long-Term Histology Cohort with Ishak Fibrosis score 4 or greater at baseline (n=10)

Nucleoside-naïve patients from:

ETV-022 HBeAg(+)	Subset of 901 rollover study
ETV-027 HBeAg(-)	• Minimum of 3 years ETV therapy • Adequate baseline and long-term biopsies • Baseline Knodell necroinflammatory score of ≥2



- All patients received:
  - ETV 0.5 mg once daily in studies ETV-022 or -027
  - ETV 1 mg once daily in ETV-901
- Qualifying long-term biopsies collected at week 288 ± 24 weeks

Analysis 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 to baseline
- Change from baseline in:
  - Ishak fibrosis score
  - Knodell necroinflammatory score
  - histologic activity index (HAI)
- Proportions with:
  - HBV DNA <300 copies/mL by PCR
  - alanine aminotransferase (ALT) ≤1 x ULN
- Statistical Analysis:
  - All data analyses are descriptive

Results

Table 1. Demographics and Baseline Characteristics: Subset with Advanced Fibrosis or Cirrhosis

	Patients with Advanced Fibrosis/Cirrhosis (n=10)
Age, mean (years)	49.5
Male (n)	10
Race: Asian (n)	4
HBeAg(+) (n)	7
HBV DNA by PCR, mean (log_{10} copies/mL)	8.7
ALT, mean (U/L)	168
Mean Knodell Necroinflammatory Score	13.7
Mean Ishak Fibrosis Score	4.6
HBV genotype (n) A B C D Other	 2 1 3 3 1

Time on therapy

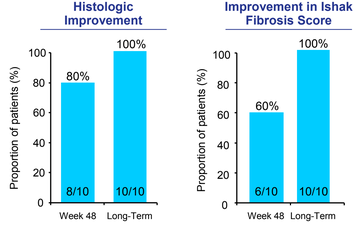
- Median exposure time on ETV treatment from phase 3 baseline to the long-term biopsy was 277 weeks (min 267, max 297)
  - Due to the ongoing blinding of Phase 2-3 studies, 8/10 patients received a brief period of concurrent ETV plus LVD early in study ETV-901 for a median of 30 weeks.
- All patients in the subset with advanced fibrosis or cirrhosis (n=10) had long-term biopsy samples obtained at the Week 288 window

Table 2. Virological, Biochemical and Histological Response in Patients with Advanced Fibrosis/Cirrhosis

	Advanced Fibrosis/Cirrhosis Subset (n=10)	
	Week 48	Long-term
Histologic improvement, n	8	10
Improvement in Ishak fibrosis score (≥1 point decrease), n	6/10	10/10
HBV DNA <300 copies/mL, n	10/10	10/10
ALT <1 x ULN, n	7/10	9/10

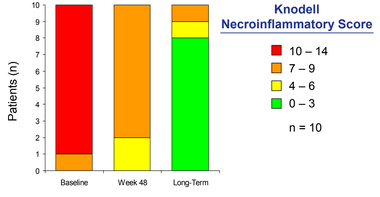
- Mean/median change from baseline in Ishak fibrosis score at week 48: -0.8/-1.0, and long-term: -2.2/-1.5
- Improvement in Ishak fibrosis score in cirrhosis patients (n=4) at week 48: 1/4, and long term: 4/4
- Median reduction in Ishak fibrosis score from baseline in cirrhosis patients at week 48: 0 (range: -1 to 0), and long-term: -3 (range: -1 to -4)

Figure 1. Histologic Response at Year 1 and Long-Term



- Following 48 weeks of ETV treatment, the majority (8/10) of patients achieved histologic improvement
  - The proportion of patients who achieved histologic improvement increased to 10/10 at Week 288 (6 years)
- Improvement in Ishak Fibrosis score was observed in 6/10 of patients following 48 weeks of ETV treatment
  - This increased to 10/10 at Week 288 (6 years)

Figure 2. Distribution of Knodell Necroinflammatory Scores at Baseline, Year 1, and Year 6



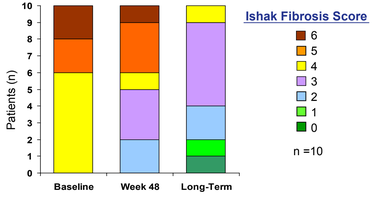
- The figure above shows the distribution of Knodell necroinflammatory scores at baseline, at Week 48, and at the time of the long-term biopsy (6 years; Week 288).
- After long-term entecavir therapy, the majority of patients in the subset with advanced fibrosis/cirrhosis at baseline (8/10) achieved a Knodell score of between 0 and 3.

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

	Advanced Fibrosis/Cirrhosis Subset (n = 10)	
	Week 48	Long-Term
Mean change from baseline in Knodell necroinflammatory score	-3.3	-7.6
Mean change from baseline in HAI*	-3.5	-8.9

*HAI: sum of the Knodell necroinflammatory and Knodell fibrosis scores

Figure 3. Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Year 6



- The figure above shows the distribution of Ishak fibrosis scores at baseline, at Week 48 and at the time of the long-term biopsy (6 years; Week 288±24 weeks).
- After long-term entecavir therapy, all the patients in the subset with advanced fibrosis/cirrhosis at baseline (10/10) achieved an improvement in Ishak fibrosis score.

Figure 4. Improvement in Ishak Fibrosis Scores in Individual Patients

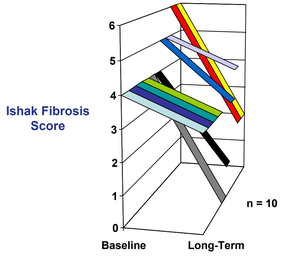
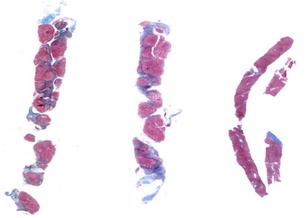


Figure 5. Case: Reduction in Fibrosis Following Long-term ETV Therapy



- 60 year old white male, HBeAg(-), baseline cirrhosis
- Baseline: fibrotic tissue stained blue (Masson trichrome stain) due to excess collagen
- Week 268: blue color scant due to reduction in collagen levels and fibrotic tissue

Table 4. Cumulative Safety Information*

	n
Any adverse event	10§
Grade 3–4 adverse event	2
Serious adverse event	2
Discontinuation due to adverse event	0
All deaths	1‡
On-treatment ALT flare±	0

* Safety was evaluated from entry in Study ETV-901 to date of data base lock (04/28/08)
§ Most common AEs, occurring in ≥2 pts: cough, bronchitis, bronchospasm, pyrexia, upper respiratory tract infection, hypertension, diabetes mellitus, myocardial ischemia, benign prostatic hyperplasia
‡ 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

Summary of Results

- All patients in the advanced fibrosis/cirrhosis subset of the Long-term Histology Cohort demonstrated histologic improvement and improvement in fibrosis at the time of long-term biopsy
- Mean change in Ishak fibrosis score was -2.2
- Mean change in Knodell necroinflammatory and HAI scores were -7.6 and -8.9, respectively
- At the time of long-term biopsy (6 years):
  - All patients had HBV DNA <300 copies/mL
  - 9/10 of patients had ALT <1 x ULN
- For the four patients with cirrhosis at baseline (Ishak score ≥5), median change in Ishak fibrosis score was a 3-point decrease (range: -1 to -4)

Conclusion

Long-term treatment with ETV for chronic hepatitis B patients with advanced fibrosis or cirrhosis results in histologic improvement and regression of fibrosis/cirrhosis

References

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Disclosure

1. Suzanne Beebe, Bruce Kreter, Dong Xu, Melissa Harris, Hong Tang, Uchenna Iloeje - Bristol-Myers Squibb employees.
2. Eugene Schiff – provided services for Abbott, Anadys, Bayer, Boehring Ingelheim, Bristol-Myers Squibb, Conatus, Daiichi-Sankyo, Debio Pharma, Gilead, GlobeImmune, Idenix, Johnson and Johnson, Merck, Novartis/Idenix, Pfizer Roche, Salix Pharmaceuticals, Sanofi Aventis, Vertex, Schering – Plough, Wyeth.
3. Samuel Lee – Consultant/Advisor/Grant/Research Support/Speakers Bureau: Bristol-Myers Squibb.
4. Fernando Bessone – Consultant/Advisor: Schering Plough, Bristol-Myers Squibb; Speakers Bureau: Bristol-Myers Squibb.
5. Adrian Gadano – Advisor: Bristol-Myers Squibb
6. The following people have nothing to disclose: SeungKew Yoon, Wieslaw Kryczka, Yoav Lurie, George Kitis, You-Chen Chao, and Shun-Sheng Wu.

Bristol-Myers Squibb