Poster Number 893

Five Years of Continuous Entecavir for Nucleoside-naïve HBeAg(+) Chronic Hepatitis B: Results from Studies ETV-022/-901

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Introduction

- The goals of treatment of chronic hepatitis B (CHB) are to achieve sustained suppression of hepatitis B virus (HBV) replication and remission of liver disease[1]
- Development of drug resistance poses a serious challenge to effective long-term treatment[2]
- Entecavir (ETV) 0.5 mg daily demonstrated superior virologic, histologic and biochemical activity compared to lamivudine (LVD) 100 mg daily in nucleoside-naïve HBeAg(+) CHB patients (study ETV-022)[3]
- Through 96 weeks, emergence of genotypic resistance to ETV was detected in only one patient[4]
- Patients who completed treatment in ETV-022 could enroll in the rollover study ETV-901
- We present long-term efficacy, safety and resistance data from a cohort of nucleoside-naïve patients from studies ETV-022 and ETV-901 who received up to 5 years of continuous therapy with ETV

Methods

Study population

- The HBeAg(+) ETV Long-term Cohort consists of patients who:
  - were initially treated with ETV in ETV-022
  - subsequently enrolled in ETV-901 with a ≤35 day treatment gap between ETV-022 and ETV-901

ETV-022 patients enrolling in ETV-901	183
Patients with treatment gap of >35 days	37
Patients with treatment gap of ≤35 days (HBeAg(+) ETV Long-term Cohort)	**146**

- The HBeAg(+) ETV Long-term Cohort is an observational cohort that was defined without regard to:
  - treatment response at end of dosing in ETV-022
  - HBV DNA, ALT measurements or HBV serology at the start of dosing in ETV-901
- Initially, due to ongoing blinding of Phase 2-3 studies, patients enrolling into study ETV-901 received a combination of ETV 1 mg and LVD 100 mg daily. Subsequently, the protocol was amended for patients to receive monotherapy with ETV 1 mg daily

Efficacy, safety and resistance analyses

- Efficacy assessments evaluated the proportions of patients who had evaluable samples at annual time points (Weeks 48, 96, 144, 192 and 240 [Non-completer = Missing]) for the following parameters:
  - HBV DNA <300 copies/mL by PCR
  - ALT ≤1 x ULN
  - HBeAg loss
  - HBe seroconversion
  - HBsAg loss
- HBV DNA measurements were performed at a central laboratory; ALT measurements were performed at local laboratories. HBV serologies were performed at a central laboratory in ETV-022 and at local laboratories in ETV-901
- Patients in the HBeAg(+) ETV Long-term Cohort were part of the ETV resistance monitoring program[5]:
  - Genotyping was performed on paired baseline and on-treatment samples from all patients who had:
    - HBV DNA ≥300 copies/mL (50 IU/mL) at Years 1, 2, 3, 4, 5 or end of dosing
    - virologic breakthrough (confirmed ≥1 $\log_{10}$ increase in HBV DNA from nadir) while on treatment
  - Phenotypic susceptibility was performed for all:
    - virologic breakthrough samples
    - isolates with novel emerging substitutions
- Safety was assessed by the incidence of clinical adverse events (AEs) and laboratory abnormalities

Results

Study population

Table 1: Demographics and Baseline Characteristics

	ETV-022 (n=354)	HBeAg(+) ETV Long-term Cohort (n=146)
Age, mean (years)	35	36
Male (%)	77	80
Race:		
Asian (%)	58	64
Non-Asian (%)	42	36
HBV DNA by PCR, mean ($\log_{10}$ copies/mL)	9.62	9.91
ALT, mean (U/L)	140	122
HBV genotype (%)		
A	13	13
B	27	26
C	31	30
D	19	27
Other	10	4

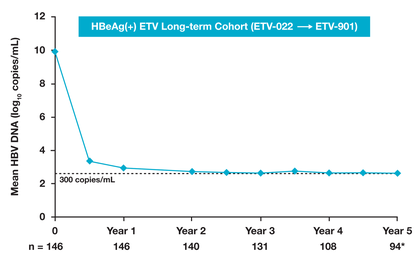
- Demographics and baseline characteristics for patients in the HBeAg(+) ETV Long-term Cohort were consistent with those of all treated patients in ETV-022

Exposure

- Fourteen patients received ETV monotherapy only for a mean of 193 weeks (median 196 weeks); 132 patients received ETV and LVD combination therapy for a mean of 26 weeks (median 24 weeks) followed by ETV monotherapy for a mean of 194 weeks (median 221 weeks)
- A total of 47 patients discontinued treatment before the Year 5 visit
- The reasons for patient discontinuation included:
  - subject withdrew = 14 (30%)
  - completed Treatment = 12 (26%)
  - death = 5 (11%)
  - other = 16 (34%)
- Among patients who discontinued treatment prior to the Year 5 visit, 37 (79%) had HBV DNA <300 copies/mL at their last visit

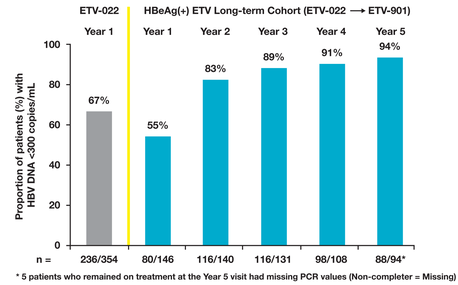
HBV DNA suppression

Figure 1: HBV DNA suppression



* 5 patients who remained on treatment at the Year 5 visit had missing PCR values (Non-completer = Missing)

Figure 2: Proportion of Patients Achieving HBV DNA <300 copies/mL Through 5 Years



* 5 patients who remained on treatment at the Year 5 visit had missing PCR values (Non-completer = Missing)

- Results at Year 1 were consistent between the HBeAg(+) ETV Long-term Cohort (55%) and the overall ETV-022 population (67%)
- Treatment in Year 2 resulted in increasing proportions of patients achieving HBV DNA <300 copies/mL
- Continuous treatment through Years 3, 4 and 5 resulted in high proportions of patients maintaining HBV DNA <300 copies/mL

ALT normalization

- Results at Year 1 were consistent between the HBeAg(+) ETV Long-term Cohort (65%) and the overall ETV-022 population (68%)
- Treatment in Year 2 resulted in increasing proportions of patients achieving ALT normalization (78%: 109/140)
- Continuous treatment through Years 3, 4 and 5 resulted in maintenance of ALT normalization (80%: at year 5)

Serologic response

- In ETV-022, 31% and 5% of patients achieved HBe seroconversion and HBsAg loss respectively through 120 weeks of on/off-treatment follow-up
- Due to protocol-defined management criteria, most patients who achieved HBeAg loss or HBe seroconversion in ETV-022 discontinued study therapy and did not enroll in the HBeAg(+) ETV Long-term Cohort
- Among the 146 patients in the HBeAg(+) ETV Long-term Cohort:
  - Five patients achieved HBe seroconversion in ETV-022
  - Continuous treatment of patients in this cohort resulted in 33 additional patients achieving HBe seroconversion in ETV-901 (on treatment and during 6 months of post-treatment follow-up)
  - Similarly, one patient achieved HBsAg loss during treatment in ETV-022 and two addtional patients achieved HBsAg loss through continued treatment in ETV-901

Resistance analysis

- One of the 146 patients in this cohort had ETV resistance (Year 3). This patient also experienced virologic breakthrough
  - Among the 47 patients who discontinued ETV prior to the Year 5 visit, 10 patients had HBV DNA ≥300 copies/mL at the last on-treatment measurement
    - Genotypic analysis showed that none had evidence of genotypic ETVr

Safety

Table 2: Cumulative Safety of Patients in the HBeAg(+) ETV Long-term Cohort (n=146)

	n (%)
Any adverse event*	133 (91)
Grade 3–4 adverse event	24 (16)
Serious adverse event	20 (14)
Discontinuation due to adverse event	0 (0)
All deaths†	5 (3)
On-treatment ALT flare‡	1 (<1)

* Most common Adverse Events, occurring in ≥10% of pts: Upper respiratory tract infection (31%), headache (21%), cough (17%), diarrhea (16%), influenza (17%), nasopharyngitis (16%), pyrexia (12%), upper abdominal pain (10%)
† Causes of death were: liver failure (1 patient); motorbike accident (1 patient); car accidents (2 patients); unknown (1 patient). No deaths were attributed to study therapy by the investigator
‡ ALT flare = ALT >2 x Baseline ALT and >10 x ULN

Summary of Results

- Ninety four percent of nucleoside-naïve HBeAg(+) patients who received 5 years of continuous treatment with ETV had HBV DNA <300 copies/mL
- Long-term treatment also resulted in maintenance of ALT normalization and incremental patients achieving HBeAg loss and HBe seroconversion
- As previously reported, only one patient in this cohort developed genotypic resistance to ETV[5]
- Safety profile remained consistent with the previously reported experience

Conclusion

- Observations from this cohort demonstrate that long-term treatment with ETV results in durable suppression of HBV DNA replication

Durable suppression with long-term ETV results in regression of fibrosis/cirrhosis **(see Poster 894)**

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Study Group

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