GS06

A PHASE 3 STUDY OF TENOFOVIR ALAFENAMIDE COMPARED WITH TENOFOVIR DISOPROXIL FUMARATE IN PATIENTS WITH HBEAGNEGATIVE, CHRONIC HEPATITIS B: WEEK 48 EFFICACYAND SAFETY RESULTS

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Background and Aims:
Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), is more stable in plasma and enhances delivery of TFV into lymphoid cells and hepatocytes while lowering circulating levels of TFV by approximately 90% compared to TDF. In patients with HIV, a TAF-containing regimen demonstrated efficacy similar to that of TDF with significantly reduced bone and renal effects (Lancet 2015; 385: 2606-15).

Methods:
In this Phase 3 study (NCT01940341), patients with HBeAgnegative, chronic hepatitis B (CHB) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 96 weeks. After Week 96, patients receive open-label TAF for 48 weeks. The primary efficacy analysis was the percent of patients with HBV DNA <29 IU/mL at Week 48; the study was powered to demonstrate non-inferiority in efficacy of TAF compared to TDF, with a 10% margin. Key pre-specified secondary safety endpointswere assessed sequentially: changes in hip and spine bone mineral density (BMD), changes in serum creatinine (sCr), and dipstick proteinuria. Markers of bone formation and resorption, and renal tubular function were also assessed. Viral resistance was evaluated by population sequencing those patients with virologic breakthrough, or viremia at time of discontinuation.

Results:
425 patients were randomized and treated at 105 sites in 17 countries. Baseline characteristics included: mean age 46 years, 61% males, 72% Asians, genotypes A through D (5%, 24%, 38%, 31%); 19% had HBV DNA ≥ 7 log10 IU/mL, and 21% were previously treated with nucleos(t)ides. Key efficacy and safety end points are summarized in the Table. At Week 48, TAF was non-inferior in efficacy to TDF with virologic response rates of 94.0% with TAF and 92.9% with TDF (difference in proportions: +1.8%, 95% CI, −3.6% to +7.2%). A greater percentage of patients treated with TAF also achieved normalization of serum ALT values. Patients on TAF experienced significantly less declines in hip and spine BMD than TDF. No

differences were seen in sCr change and proteinuria; however, smaller declines in eGFRCG and smaller changes in renal tubular markers were observed in the TAF arm. The rates of treatment discontinuations and serious adverse events were lowand similar in the two arms. No viral resistance was observed in the 4 patients (2 per group) who qualified for testing.

n/N (%)	TAF (N=285)	TDF (N=140)	P value
HBV DNA <29 IU/mL	268/285 (94)	130/140 (92.9)	0.47
ALT normalization (Central lab)[a]	196/236 (83.1)	91/121 (75.2)	0.076
ALT normalization (AASLD)[b]	137/276 (49.6)	44/138 (31.9)	<0.001
Hip BMD, % change (g/cm²)[c]	-0.29 (2.14)	-2.16 (2.17)	<0.001
Spine BMD, % change (g/cm²)[c]	-0.88 (2.86)	-2.51 (3.36)	<0.001
Change in sCr (mg/dL)[c,d]	0.01 (0.09)	0.02 (0.10)	0.32
Proteinuria (dipstick)	54/282 (19.2)	26/140 (18.5)	0.90
Change in $eGFR_{CG}$ (mL/min)[c,e]	-1.4 (12.7)	-4.7 (12.0)	0.004

Efficacy results are missing = failure
[a]ULN 43 U/L males, 34 U/L females; [b]ULN 30 U/L males, 19 U/L females; [c]Mean (SD);
[d]sCr is serum creatinine; [e]$eGFR_{CG}$ is CL_{Cr} (Cockcroft-Gault)

Conclusions:
Compared to TDF 300 mg, the efficacy of TAF 25 mg in patients with HBeAg-negative CHB was non-inferior. Safety was also improved, with less change in bone and renal parameters.