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Reduced Bone Mineral Density Derived from Dual X-ray Absorptiometry (DEXA) Assessments in Patients with Chronic Hepatitis B (CHB)

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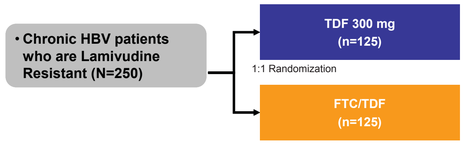
Introduction

- Lamivudine (LAM) is used extensively worldwide for the treatment of chronic HBV but is associated with a high rate of resistance, approaching 70% after 4 years of therapy[1]
  - Chronic HBV treatment guidelines recommend adding tenofovir disoproxil fumarate (TDF) or switching to TDF/emtricitabine (FTC) in the setting of confirmed LAM-resistance[1,2]
- Study GS-US-174-0121 compares the safety and efficacy of TDF to TDF/FTC in chronic HBV subjects currently receiving LAM monotherapy with LAM- associated resistance mutations
- Metabolic bone disease is a known complication of chronic liver disease
  - Little data are available specific to patients with chronic hepatitis B
- **Objective** of the current analysis is to assess the prevalence of bone disease at baseline (prior to treatment initiation) in Study GS-US-174-0121 based on DEXA scans

Methods

Figure 1. GS-US-174-0121 Study Design

- Phase 3b, Randomized, double-blind, placebo-controlled trial
- Total Study Duration: 240 Weeks (5 Years)



Stratification: HBeAg status (negative or positive) and ALT level (≥ 2 × ULN or < 2 × ULN) at screening

- Bone mineral density (BMD) of the hip and spine was assessed by DEXA scans at study sites with DEXA capabilities at baseline, every 6 months in the first 2 years, and then annually
- BMD can be expressed as T-Score or Z-Score values and are expressed as standard deviation (SD) above or below their average values

Table 1. Diagnostic Classification

The World Health Organization (WHO)[3]: T-Score	
Terminology	**T-Score Definition**
Normal	T≥ -1.0
Osteopenia	-2.5<T<-1.0
Osteoporosis	T≤ -2.5
Established osteoporosis	T≤-2.5 in the presence of one or more fragility fractures
Calculation of T-Score	T-score= (Measured BMD - Young adult mean BMD) / Young adult population SD
International Society for Clinical Densitometry[4]: Z-Score	
Z-score	-2.0 or less defined as "below the expected range for age"
Calculation of Z-Score	Z-score= (Measured BMD - Age matched mean BMD) / Age matched population SD

Key Inclusion Criteria:

- 18-75 yo age
- CHB patients defined as positive serum HBsAg for at least 6 months
- HBV DNA ≥ 10^3 copies/mL
- Current LAM use with confirmation mutation known to confer resistance to lamivudine (rtM204I/V with or without rtL180M); up to 48 weeks of prior/concurrent Adefovir (ADV) use permitted
- CrCl ≥ 50 mL/min (Cockcroft-Gault method)
- ALT <10 x ULN
- Compensated liver disease
- HIV-1, HDV, and HCV seronegative

Results (cont'd)

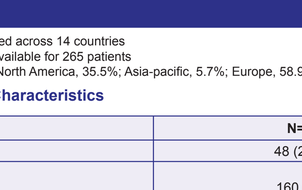
- 280 patients were enrolled across 14 countries
- Baseline DEXAs were available for 265 patients
- Enrolment by Regions: North America, 35.5%; Asia-pacific, 5.7%; Europe, 58.9%

Table 2. Baseline Characteristics

Characteristics*	N=265
Age (yrs)	48 (20, 73)
Race (%): White Asian Black Pacific Islander Other	 160 (60.4) 94 (35.5) 4 (1.5) 2 (0.8) 5 (1.9)
Male (%)	199 (75.1)
Weight (Kg)	75 (46, 132.1)
Height (Cm)	170 (148, 208.3)
BMI (Kg/m^2)	25.1 (17.1, 40.5)
HBV DNA (log$_{10}$ c/mL)	6.5 (2.5, 10.1)
ALT (U/L)	50 (8, 1302)
HBeAg Positive (%)	126 (48)
Medical History	**N (%)**
Thyroid Diseases	5 (1.9 %)
Fracture	5 (1.9%)
Concomitant Medications	**N (%)**
Thyroid Therapy (Levothyroxine)	4 (1.5)
Tamoxifen	1 (0.4)
Proton Pump Inhibitors	11 (4)
Calcium or calcium + vitamin D	16 (6%)
Treatment of Bone Disease (Bisphosphonates)	3 (1)
Hormone Replacement Therapy	1 (0.4)

*Data reported as Median (Range)

Figure 3. Baseline Bone Status Based on Medical History



*1 patient reported as having low bone density & 1 patient reported as having borderline osteopenia

Figure 4. Baseline BMD (Based on T-Scores)

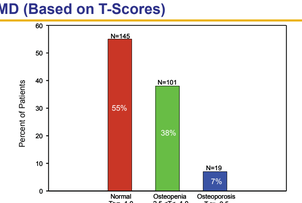


Table 3. Baseline Demographics for Patients with Medical History of Osteopenia/ Osteoporosis (see Fig 3)

Osteopenia (N=6)	Age (range) Gender Race	47-66 yo 2 Female, 4 Male 5 Asian, 1 White
Osteoporosis (N=4)	Age (range) Gender Race	50-58 yo 3 Female, 1 Male 4 Asian

Table 4. Baseline Characteristics Based on T-Score (see Fig 4)

Characteristics*	Normal (n=145)	Osteopenia (n=101)	Osteoporosis (n=19)
Region North America Asia-Pacific Europe	 33.8% 5.5% 60.7%	 36.6% 5.9% 57.4%	 42.1% 5.3% 52.6%
Age	47 (20, 73)	49 (20, 71)	53 (20, 72)
Male	106 (73.1%)	81 (80.2%)	12 (63.2%)
Female Menopause	39 (26.9%) 27 (69.2%)	20 (19.8%) 9 (45.0%)	7 (36.8%) 3 (42.9%)
Race White Asian	92 (63.4%) 45 (31.0%)	59 (58.4%) 39 (38.6%)	9 (47.4%) 10 (52.6%)
Weight (Kg)	77.4 (47.1, 132.1)	72.0 (48.0, 119.4)	64.0 (46.0, 90.0)
BMI (Kg/m^2)	26.2 (17.1, 40.5)	24.6 (17.3, 37.9)	23.5 (20.2, 29.1)
Height (cm)	171.3 (150.0, 208.3)	170.0 (148.0, 198.0)	165.0 (151.0, 176.0)
HBV DNA (log$_{10}$ c/mL)	6.4 (2.5, 10.1)	6.7 (3.2, 9.5)	5.2 (2.9, 8.9)
HBeAg Positive	56 (38.6%)	59 (58.4%)	11 (57.9%)
ALT (U/L)	51 (15, 844)	50 (12, 1302)	40 (8, 905)
Cirrhosis	4 (2.8%)	1 (<1%)	0
Years Since HBV Diagnosis	8.5 (1.2, 34.9)	8.1 (1.5, 33.1)	14.7 (2.9, 35.0)
Years Since First HBV Treatment	3.8 (0.7, 22.8)	4.2 (0.8, 16.0)	3.9 (1.1, 10.9)
Years of LAM Treatment	3.4 (0.7, 12.4)	3.5 (0.7, 15.9)	3.5 (0.1, 6.8)
Number of patients with prior ADV treatment	34 (23.4%)	20 (19.8%)	6 (31.6%)
Years of ADV Treatment	0.9 (0.1, 2.7)	0.9 (0.1, 3.9)	0.8 (0.5, 3.5)
Number of Years of Alcohol Consumption	0 (0, 50)	0 (0, 50)	0 (0, 45)

*Data reported as Median (Range)

Figure 5. Median Baseline T-Score of Spine

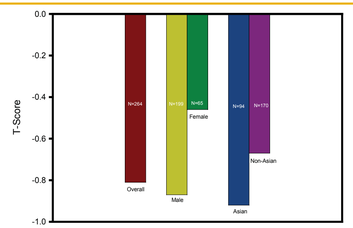


Figure 6. Median Baseline T-Score of Hip

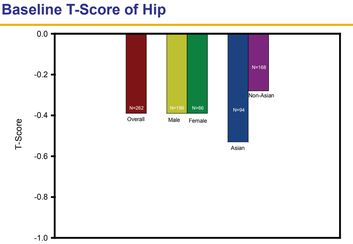


Table 6. Patients with Baseline Z-Score <=-2

Spine: 24/269 (8.9%)		Hip: 5/267 (1.9%)	
Asian	11/24 (46%)	Asian	3/5 (60%)
Male <50 yrs Asian	19/24 (79%) 14/19 (74%) 7/19 (37%)	Male <50yrs Asian	4/5 (80%) 3/4 (75%) 2/4 (50%)
Female Post Menopausal Asian	5/24 (21%) 3/5 (60%)	Female Post Menopausal Asian	1/5 (20%) 1/1 (100%)

Figure 7. Median Baseline Z-Score of Spine in Females

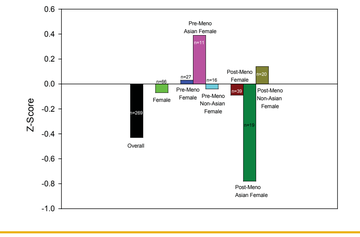
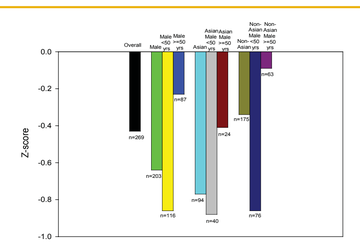


Figure 8. Median Baseline Z-Score of Spine in Males



Summary

- Higher prevalence of reduced BMD was observed in our study population prior to study entry based on DEXA scans compared to reported medical history
- Duration of chronic HBV infection and HBeAg status could contribute to high prevalence of reduced BMD; However, treatment duration (LAM, ADV) appears to not contribute to reduced BMD
- In our study, baseline median Z and T- scores suggest that males and Asians have greater reductions in BMD compared to females and non-Asians
  - Limitations: single DEXA timepoint and number of subjects in sub-population categories were small

Conclusions

- **Our data demonstrate a higher prevalence of baseline bone disease among patients with chronic HBV.**
- **Duration of chronic HBV but not duration of treatment appears to impact BMD**
- **Additional studies to further characterize bone disease in chronic HBV population are warranted**

References

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