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Interim Results of a Randomized Treatment Study of Emtricitabine/Tenofovir DF (FTC/TDF) and HBIG Withdrawal in Post-Orthotopic Liver Transplant (OLT) Recipients for CHB

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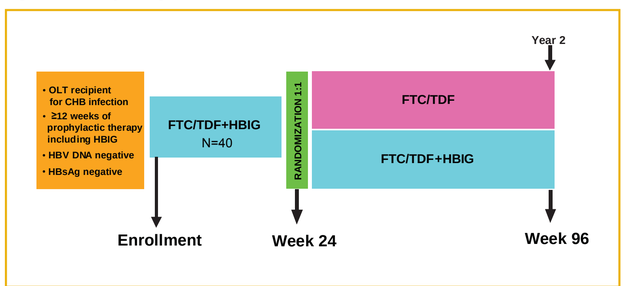
Introduction

- HBIG prophylaxis prevents HBV recurrence post-OLT by neutralizing HBsAg and is the current standard of care
- Oral antivirals combined with HBIG have reduced the risk of HBV recurrence to <10%
- Combination treatment with adefovir dipivoxil, lamivudine and HBIG has successfully prevented the recurrence of lamivudine resistant HBV post OLT[1,2]
- However, attempts to either use lamivudine monotherapy or withdraw HBIG from combination therapy results in high rates of HBV recurrence[3,4]
- Despite the established efficacy of HBIG, long-term prophylaxis is expensive and requires frequent IV or IM administration
- New potent antivirals such as FTC/TDF may provide a clinical strategy to reduce or eliminate the need for HBIG

Primary Objectives

- This ongoing Phase 2 randomized study evaluates the safety and efficacy of FTC/TDF with/without HBIG in preventing recurrence of CHB post OLT
- The aim of this preliminary analysis is to evaluate the efficacy, safety, and tolerability of FTC/TDF in this population

Figure 1. Study Design



FTC + TDF is given as a fixed-dose combination tablet (Truvada) taken once daily

Methods

- Monitor safety laboratory parameters every 8-12 weeks
- Monitor HBV DNA (Roche COBAS TaqMan assay; LLOQ=169 copies/mL) and HBsAg every 8 to 12 weeks
- Monitor Adverse Events (AEs)
- Resistance surveillance for any patient with HBV DNA ≥ 400 copies/mL

Key Eligibility Criteria

- 18–75 years of age with CHB prior to transplant
- No CHB recurrence after transplant
- Stable patients with ≥ 12 weeks of prophylactic therapy including HBIG after transplant
- Creatinine clearance ≥ 40 mL/min
- No prior TDF or FTC/TDF treatment after transplant
- HCV, HIV-1, and HDV sero-negative
- No significant renal, cardiovascular, pulmonary, or neurological disease

Results

Table 1. Baseline Disease and Demographic Characteristics

Baseline Characteristic	Overall Population N=40	Randomized FTC/TDF+HBIG N=19	Randomized FTC/TDF N=18	Discontinued Prior to Randomization N=3
Median Age (min, max)	59 (37, 73)	55 (38, 73)	61 (37, 71)	65 (58, 70)
Race, n (%): Asian White Black Other	15 (38) 13 (33) 10 (25) 2 (5)	6 (32) 7 (37) 5 (26) 1 (5)	8 (44) 5 (28) 4 (22) 1 (6)	1 (33) 1 (33) 1 (33) 0
Male, n (%)	32 (80)	15 (79)	15 (83)	2 (67)
Median ALT U/L (min, max)	21.0 (10, 58)	19.0 (10, 43)	21.0 (15, 58)	25.0 (23, 34)
Median years since transplant (min, max)	3.4 (0.3,17.7)	3.1 (0.3,17.7)	3.4 (0.4, 9.5)	5.9 (5.0,12.5)
HBeAg negative prior to transplant, n (%)	25/34 (74)	11/17 (65)	12/15 (80)	2/2 (100)

Figure 2. Patient Disposition

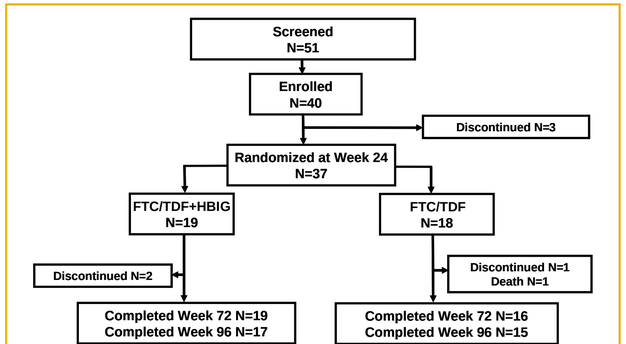


Table 2. Patient Disposition and Exposure by Baseline Renal Function

	Baseline Creatinine Clearance			
	Overall N	<50 mL/min	50-80 mL/min	>80 mL/min
Number of Patients Enrolled	40	9	24	7
# Patients Randomized to FTC/TDF+HBIG	19	3	13	3
# Patients Randomized to FTC/TDF	18	5	11	2
# Patients not randomized*	3	1	0	2
Number of Patients Randomized by Week in Study				
Week 72	35	8	22	5
Week 96	32	7	20	5

*Patients discontinued study drug on or before week 24

Table 3. Summary of Safety Data

	Overall N=40	Randomized FTC/TDF+HBIG N=19	Randomized FTC/TDF N=18	Prior to Randomization N=40
Study Drug Discontinuation due to AE/Death	3 (8)	1(5.3)	1 (6)	1 (2.5)
Serious AE (SAE) • considered related to FTC/TDF	10 (25) 0	6(31.6) 0	3 (17) 0	2 (5) 0
Grade 3 or 4 AE • considered related to FTC/TDF	7 (17.5) 0	5 (26) 0	2 (11) 0	0 0
Grade 2 − 4 AE • considered related to FTC/TDF	25 (62.5) 2 (5)	11(58) 0	8 (44)	9 (23) 2 (5)

Study Drug Discontinuation resulting from AE:
- Increase in ALT/AST
- Worsening in Colitis

Table 4. Summary of Grade 3/4 Laboratory Abnormalities

	Overall Population N=40	Randomized FTC/TDF+HBIG N=19	Randomized FTC/TDF N=18	Prior to Randomization N=40
Total # of Pts with Grade	13 (32.5)	7 (37)	1 (6)	7 (18)
Hyperglycemia	3 (8)	0	0	3 (8)
Hypernatremia	2 (5)	1 (5)	1 (6)	0
Glucosuria	4 (8)	1 (5)	0	3 (8)
Leucopenia	2 (5)	1 (5)	0	1 (3)
Thrombocytopenia	1(3)	1 (5)	0	0
Transaminitis	2 (5)	2 (11)	0	0
Hyperbilirubinemia	2 (5)	1 (5)	0	1 (3)
Prothrombin Time	3 (8)	2 (11)	0	1 (3)
Creatine Kinase	1 (3)	1 (5)	0	0

Table 5. Summary of Renal Safety

	Baseline Creatinine Clearance		
Confirmed Treatment-Emergent Parameters	**<50 mL/min N=9**	**50 to 80 mL/min N=24**	**>80 mL/min N=7**
Phosphorus <2 mg/dL	0	0	0
0.5 mg/dL increase in creatinine	0	1 (4)	0
Creatinine clearance < 50 mL/min	NA	6 (25%)	0

Figure 3. Creatinine Clearance Over Time

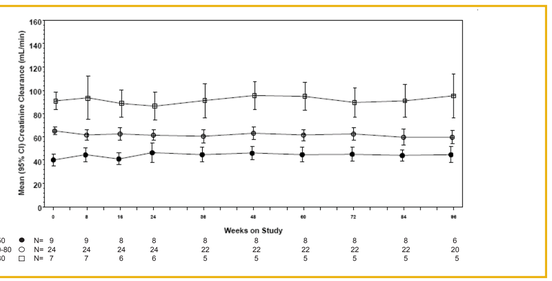
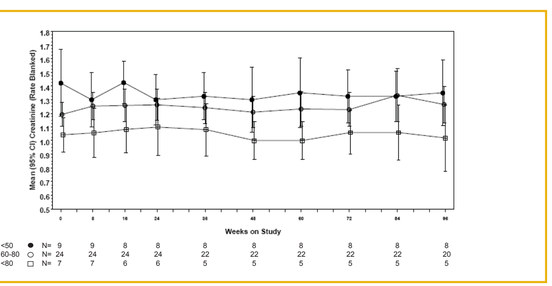


Figure 4. Serum Creatinine Over Time



Virologic Outcomes

- All patients maintained HBV DNA below LLOQ during the study period
  - No evidence of HBV recurrence
  - No re-initiation of HBIG after withdrawal for persistent viremia or virologic breakthrough
- Subject remained HBsAg negative
- No subject demonstrated evidence of resistance to FTC/TDF

Conclusions

- **FTC/TDF is well tolerated in post-OLT patients**
- **Serum creatinine and creatinine clearance remained stable on FTC/TDF treatment in post-OLT patients**
- **No patient on FTC/TDF who discontinued HBIG had detectable HBV DNA or HBsAg**

References

1. Marzano et al. Liver Transpl 2005
2. Lo et al. Liver Transpl 2005
3. Naoumov et al. J Hepatol 2001
4. Zheng et al. Liver Transpl 2006