No Detected Resistance to Tenofovir Alafenamide (TAF) Through 96 Weeks of Treatment in Children and Adolescents With Chronic Hepatitis B

1429-C

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Key Findings

- **Among 88 pediatric patients treated with TAF for 2 years (96 weeks), 24 (27%) qualified for sequence analysis; 12 (50%) qualified due to persistent viremia (HBV DNA ≥69 IU/mL)**
- **Of 24 patients, 17 (71%) showed either no sequence change in pol/RT from baseline or were unable to be sequenced at week 96; conserved site changes were observed in only 3 (13%) patients**
- **Week 96 isolates from the patients who qualified for phenotypic analysis (n = 5) remained sensitive to TAF in vitro (<2-fold change in EC_{50} vs baseline)**

Conclusions

No resistance to TAF was detected through 96 weeks of treatment in adolescents and children with CHB

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Introduction

- Children and adolescents with chronic hepatitis B (CHB) have an increased lifetime risk for clinical complications, including progression to cirrhosis, decompensated liver disease, and liver cancer[1]
- First-line treatment options for children with CHB are generally similar to those for adults; however, there are potential safety and efficacy limitations, including reduced response rates and/or development of resistance in patients with prior lamivudine experience treated with entecavir and bone mineral density reductions (relative to placebo [PBO]) with use of tenofovir disoproxil fumarate[2-4]
- The US Food and Drug Administration recently approved tenofovir alafenamide (TAF) for the treatment of CHB in patients aged 12 and older with compensated liver disease,[5] and the European Medicines Agency recently expanded the indication for children aged 6 and older weighing ≥25 kg based on week 48 findings from a randomized, double-blind, controlled trial (GS-US-320-1092; NCT02932150) in children and adolescents[6]
- No resistance to TAF has been observed during double-blind treatment through 96 weeks[7] and through year 8 of open-label TAF treatment in adults with CHB[8]; likewise, no resistance to TAF was detected in adolescents and children with CHB through 48 weeks of TAF treatment[9]

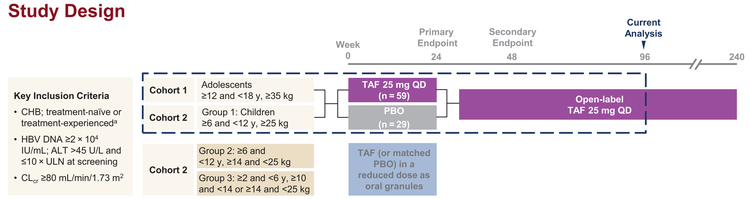
Objective

- To assess the potential for resistance development at week 96 in a Phase 2 study evaluating the adult dose of TAF treatment (25 mg once daily [QD]) when given to adolescents and children with CHB

Methods

- Randomized (2:1), double-blind, PBO-controlled, multicenter study (GS-US-320-1092; NCT02932150)
- Randomized phase: TAF 25 mg QD vs matched PBO for 24 weeks (completed for cohort 1 and cohort 2, group 1)
- Open-label extension phase: TAF 25 mg QD from weeks 24 to 240 (all patients, ongoing); treatment groups: TAF and PBO→TAF

Study Design



[a]Treatment-naïve: <12 weeks of treatment with any oral nucleos(t)ide analogue; treatment-experienced: ≥12 weeks of treatment with any oral nucleos(t)ide analogue.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; CL_{cr}, creatinine clearance; HBV, hepatitis B virus; PBO, placebo; QD, once daily; TAF, tenofovir alafenamide; ULN, upper limit of normal; y, years.

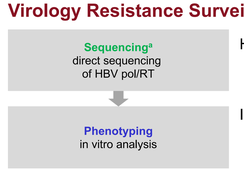
Virology Definitions

- **Virologic breakthrough:** Hepatitis B virus (HBV) DNA ≥69 IU/mL after achieving <69 IU/mL, or a ≥1.0-log_{10} increase from nadir for 2 consecutive visits
- **Virologic blip:** HBV DNA ≥69 IU/mL after achieving <69 IU/mL or a ≥1.0-log_{10} increase from nadir for 1 visit
- **Viremia:** persistent HBV DNA ≥69 IU/mL over the course of treatment in the absence of virologic breakthrough

Conserved vs Polymorphic Amino Acid Positions

- Conserved and polymorphic positions in polymerase/reverse transcriptase (pol/RT) were previously defined in patients with CHB using treatment-naïve sequences[4]
- Conserved amino acid position
  - Only 1 amino acid observed, or
  - 2 amino acids observed, 1 of which is found in <1% of sequences
- Polymorphic amino acid position
  - 2 amino acids observed, where both are found in ≥1% of sequences, or
  - More than 2 amino acids observed, even if detected in <1% of sequences

Virology Resistance Surveillance



HBV pol/RT sequencing was conducted for patients:
- With HBV DNA ≥69 IU/mL at week 96, or
- At early discontinuation if HBV DNA ≥69 IU/mL

In vitro phenotyping was performed for patients with:
- Changes at a conserved site in the HBV pol/RT
- Changes at polymorphic sites if seen in >1 patient
- Virologic breakthrough with any amino acid changes in the pol/RT of HBV

[a]Limit of sequencing assay = 69 IU/mL.
HBV, hepatitis B virus; pol/RT, polymerase/reverse transcriptase.

Results

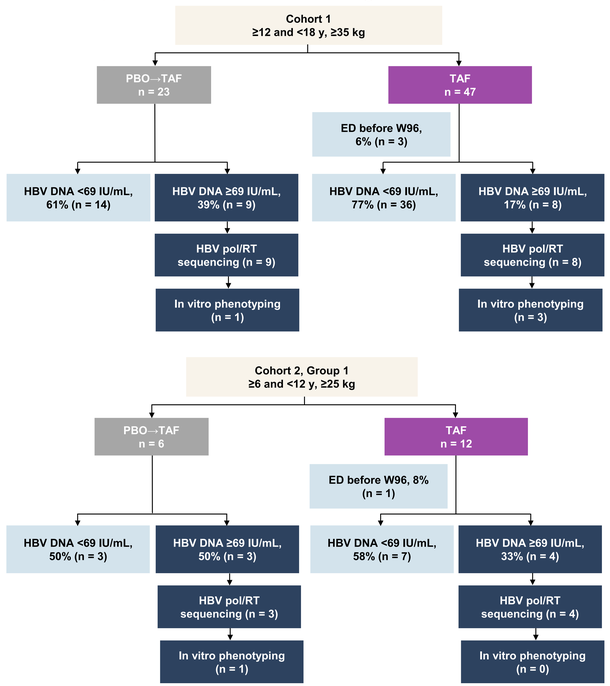
Summary of Baseline HBV Genotype Analysis

HBV Genotype	Cohort 1		Cohort 2, Group 1		Total (n = 88)
	Placebo→TAF (n = 23)	TAF (n = 47)	Placebo→TAF (n = 6)	TAF (n = 12)	
HBV genotype A	1 (4.3)	4 (8.5)	0	1 (8.3)	6 (6.8)
HBV genotype B	5 (21.7)	10 (21.3)	1 (16.7)	3 (25.0)	19 (21.6)
HBV genotype C	7 (30.4)	11 (23.4)	1 (16.7)	1 (8.3)	20 (22.7)
HBV genotype D	8 (34.8)	17 (36.2)	4 (66.7)	7 (58.3)	36 (40.9)
Mixed genotype	0	1 (2.1)	0	0	1 (1.1)
Genotype undetermined	2 (8.7)	4 (8.5)	0	0	6 (6.8)

Data are shown as n (%). HBV, hepatitis B virus; TAF, tenofovir alafenamide.

- Genotype D was the most commonly observed HBV genotype overall and represented a greater proportion in cohort 2, group 1
- Genotypes B and C were observed at similar frequencies overall and were more common in cohort 1

Patient Disposition for Resistance Testing at Week 96



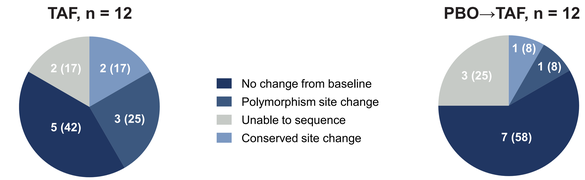
ED, early discontinuation; HBV, hepatitis B virus; pol/RT, polymerase/reverse transcriptase; PBO, placebo; TAF, tenofovir alafenamide; W, week; y, years.

Reasons for Sequence Analysis at Week 96, n (%)

HBV, hepatitis B virus; PBO, placebo; pol/RT, polymerase/reverse transcriptase; TAF, tenofovir alafenamide.

- Overall, 50% of patients qualified for sequence analysis due to persistent viremia
- Similar proportions of patients (33%) qualified for virologic breakthrough

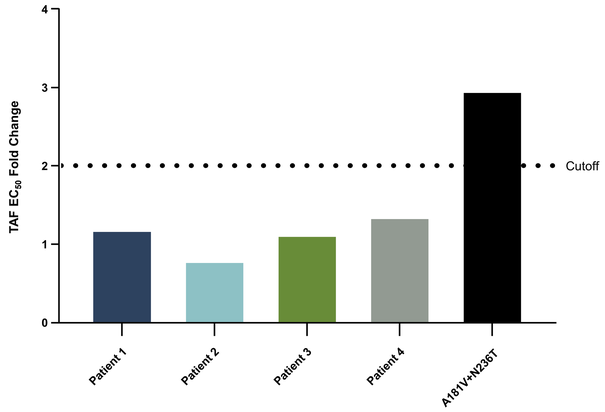
Sequence Changes in pol/RT in Patients Who Qualified for Sequence Analysis at Week 96, n (%)



PBO, placebo; pol/RT, polymerase/reverse transcriptase; TAF, tenofovir alafenamide.

- The majority of patients (17 of 24, 71%) had no sequence change from baseline or were unable to be sequenced
- Only 3 (12.5%) patients had conserved site changes
- Overall, 5 patients qualified for phenotypic evaluation at week 96 due to virologic breakthrough with any amino acid change (n = 2) or conserved site change (n = 3)

Phenotypic Evaluation of Qualified Patients With Available Data at Week 96[a]



[a]Phenotypic analysis was not performed for patient #5 due to sample unavailability. A181V+N236T is the assay control with low-level resistance to TAF in vitro.
EC_{50}, half-maximal effective concentration; TAF, tenofovir alafenamide.

- No patients demonstrated a >2-fold change in half-maximal effective concentration (EC_{50}) compared with baseline; therefore, no resistance to TAF was observed