Poster

Pharmacokinetics, safety, and efficacy of bictegravir emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV

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Introduction

- Bictegravir (BIC, B) is a novel, unboosted integrase strand transfer inhibitor (INSTI)1-3
  - Low DDI potential
  - Co-formulated with FTC and TAF as a:
    - Single tablet
    - Once daily
    - Given without regard to food
- B/F/TAF is currently approved for HIV+ adults in the US, EU, Australia, and Canada based on results of 4 Phase 3 studies in adults showing:4-7
  - High rates of viral suppression
  - No treatment-emergent resistance to B/F/TAF
- TAF–based regimens show improved bone and renal safety compared with tenofovir disoproxil fumarate (TDF)–based regimens8-9
- The pharmacokinetics (PK), safety, and efficacy of B/F/TAF in adolescents are similar to that for adults10
- We report PK, safety, and efficacy of B/F/TAF in virologically suppressed children

Objectives

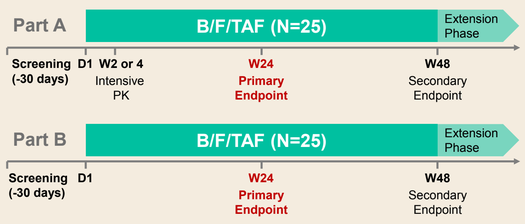
- Primary: to determine the plasma PK of BIC, and evaluate the safety and tolerability of B/F/TAF through 24 weeks of treatment in children (6 to <12 years old and ≥25 kg) living with HIV-1
- Secondary: to evaluate the safety and tolerability of B/F/TAF through 48 weeks, and its antiviral activity at 24 and 48 weeks in children living with HIV-1

Methods

Study Design: Cohort 2*

Virologically Suppressed Children, 6 to <12 yrs, ≥25 kg

Eligibility Criteria
- 6–<12 years ≥25 kg
- HIV-1 RNA <50 copies/mL for ≥6 months
- CD4 count ≥200 cells/μL
- eGFR ≥90 mL/min/1.73 m² (Schwartz)



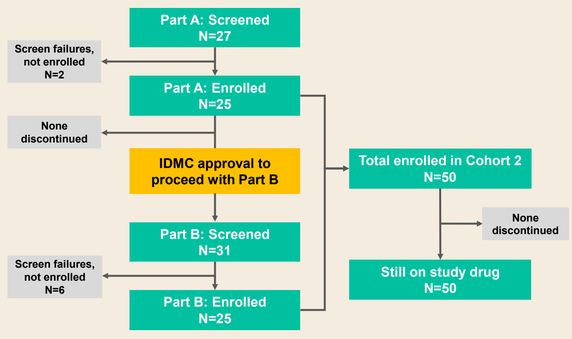
*Cohort 1 evaluated B/F/TAF in adolescents (12 to <18 years of age); results have been previously reported in Gaur A, et al. CROI 2018, #844.

- Phase 2/3, open-label, multicenter, multicohort, single-arm study (NCT02881320)
  - Part A: Intensive PK was assessed to confirm the dose of B/F/TAF (50/200/25 mg QD)
  - Part B: Following dose confirmation and IDMC review of short-term safety from Part A, additional participants were enrolled to complete the cohort

Study Assessments

- PK assessments
  - Part A: Intensive PK to confirm adequate steady-state (Wk 2 or 4) exposure of BIC as well as FTC and TAF
    - PK parameters in children (test) compared with adults (reference)
    - % geometric least-squares mean ratio (%GMR) and 90% confidence interval (CI) calculated for BIC, FTC, and TAF PK parameters
    - 90% CI for %GMR compared with predefined PK equivalence boundaries of 70-143%
- Safety assessments: Adverse events (AEs) and clinical laboratory abnormalities
- Efficacy assessments: HIV-1 RNA and CD4 cell count
- Tablet assessments:
  - Tablet acceptability/palatability case report form captured:
    - Palatability
    - Acceptability (acceptable product shape and size)
  - Investigator (or designee) used age-appropriate questions to ascertain palatability and acceptability
- Adherence: Number of pills taken divided by number of pills prescribed

Disposition: Cohort 2



- Part A enrolled in 6 days and B in 30 days

Baseline Characteristics: Cohort 2

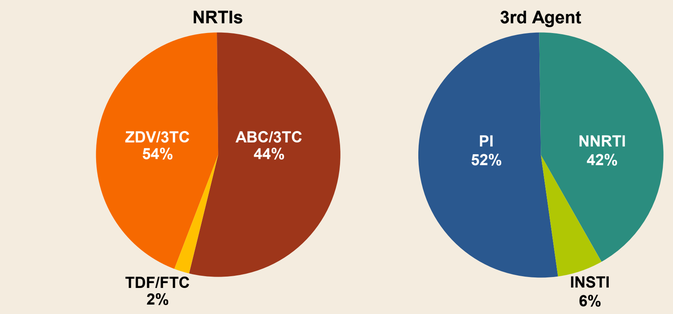
Virologically Suppressed Children, 6 to <12 yrs, ≥25 kg

		B/F/TAF, N=50
Median age, years (range)		10 (6-11)
Median weight, kg (Q1, Q3)		29.0 (26.9, 32.5)
Female, n (%)		27 (54)
Race, n (%)	Black	36 (72)
	Asian	11 (22)
	White	2 (4)
	Other	1 (2)
Country, n (%)	South Africa	20 (40)
	USA	12 (24)
	Thailand	10 (20)
	Uganda	8 (16)
HIV-1 RNA <50 copies/mL, n (%)		50 (100)
Mean CD4 cell count, /μL (SD)		930 (309.9)
Median eGFR, mL/min/1.73 m2 (Q1, Q3)		153.5 (144.0, 173.0)
Mode of transmission, n (%)	Vertical	48 (96)
	Unknown	1 (2)
	Transfusion	1 (2)
Median time since diagnosis of HIV, years (range)		10 (2-11)

eGFR, estimated glomerular filtration rate by Schwartz formula; SD, standard deviation.

Results

ARV Treatment Prior to Switching to B/F/TAF



*3TC/NVP/AZT STR. 3TC, lamivudine; ABC, abacavir; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

- 4 participants (8%) were on a twice-daily fixed-dose regimen (FDC) as a single tablet regimen (STR)*

Intensive Pharmacokinetic Data

	PK Parameter*	Cohort 2, Part A 6–<12 y; ≥25 kg†	B/F/TAF-Treated Adults‡	Children/Adults GMR% (90% CI)
BIC	AUC_{tau}, h·ng/mL	121,000 (36)	102,000 (27)	**116 (104,130)**
	C_{max}, ng/mL	11,000 (28)	6150 (23)	177 (162,194)
	C_{tau}, ng/mL	2,370 (79)	2610 (35)	78.3 (63.4, 96.7)

*Mean (% coefficient of variation); values are presented to 3 significant figures; †N=24; ‡Pooled population-PK data from 4 phase 3 studies in HIV-1 Infected adults for B/F/TAF (N=1193). AUC_{tau}, area under curve over dosing interval; CI, confidence interval; C_{max}, maximum concentration; C_{tau}, trough concentration; GMR, geometric mean ratio.

- BIC AUCtau was similar in children and adults
  - BIC Cmax was 77% higher in children
- No trends in exposure-safety were observed for BIC in phase 3 studies of B/F/TAF
  - C_{tau} was 22% lower in children compared with adults
    - Mean BIC C_{tau} (2370 ng/mL) was >14-fold above the protein-adjusted 95% effective concentration (162 ng/mL) against wild-type HIV-1 virus[1]

1. Lutz 2018 IWCPAT

Intensive Pharmacokinetic Data

	PK Parameter*	Cohort 2, Part A 6–<12 y; ≥25 kg†	B/F/TAF-Treated Adults‡	Children/Adults GMR% (90% CI)
FTC	AUC_{tau}, h·ng/mL	17,600 (37)	12,300 (29)	142 (127,159)
	C_{max}, ng/mL	3,890 (31)	2,130 (35)	185 (162, 210)
	C_{tau}, ng/mL	227 (323)	96.0 (37)	95.0 (69.9,129)
TAF	AUC_{tau}, h·ng/mL	435 (95)	229 (63)	175 (136, 226)
	C_{max}, ng/mL	582 (100)	277 (62)	170 (120, 241)

*Mean (% coefficient of variation); values are presented to 3 significant figures; †N=22–25; ‡Intensive PK data from 4 phase 3 studies in HIV-1 Infected adults for FTC (N=77) and TAF (N=77).

- Exposures of FTC and TAF were consistent with safe and efficacious ranges of historical data in adults, adolescents, and children following administration of approved FTC/TAF-containing products including EVG/COBI/FTC/TAF (Genvoya®)[1,2]

1. Descovy [package insert]. Foster City, CA: Gilead Sciences, Inc., 4/16; 2. Genvoya [package insert]. Foster City, CA: Gilead Sciences, Inc., 4/16.

Overall Safety

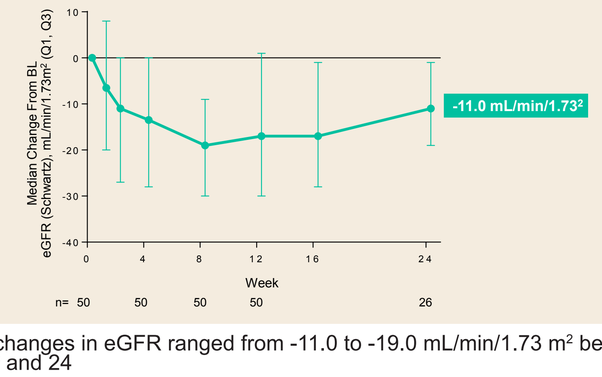
Participants, n (%)	B/F/TAF, N=50
Any grade AE	33 (66)
Grade 3/4 AE	0
Serious AE	0
AE leading to study drug D/C	0
Death	0
AE related to study drug*	6 (12)
Abdominal discomfort	1 (2)
Diarrhea	1 (2)
Fatigue	1 (2)
Decreased appetite	1 (2)
Increased appetite	1 (2)
Dizziness	1 (2)
Headache	1 (2)
Rash	1 (2)

*2 participants had 2 AEs related to study drug.

- Median (Q1, Q3) exposure to study drug: 33.6 (20.3, 46.4) weeks
- Most common AEs were upper respiratory tract infection (n=7 [14%])
  - All AEs were grade 1 or 2
- No participant discontinued due to an adverse event
- Grade 3/4 laboratory abnormalities were uncommon (n=4 [8%])

Results (con't)

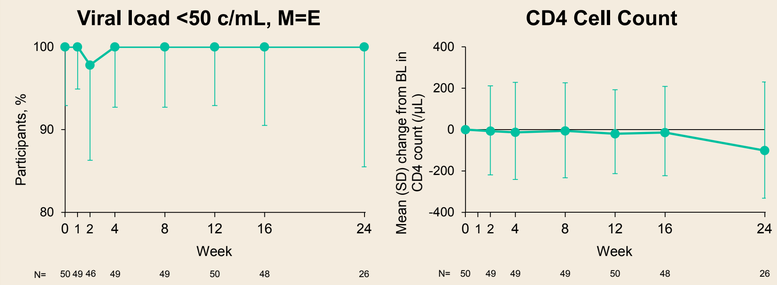
Changes in eGFR (Schwartz) Over Time



- Median changes in eGFR ranged from -11.0 to -19.0 mL/min/1.73 m² between Weeks 2 and 24
- Changes in eGFR in children were:
  - Consistent with the known renal creatinine transporter effect of BIC1,2
  - Not considered clinically significant

1. Zhang H, et al. 18th IWCPAT 2017, poster 50; 2. Zhang H, et al. British HIV Association 2017; Liverpool, UK; April 5, 2017. O2.

Efficacy: Virologic Outcome



- Maintenance of virologic suppression at Week 24: HIV-1 RNA <50 copies/mL in all 25 participants (100%, 95% CI: 86.3% to 100.0%) by US FDA Snapshot Algorithm
  - Only N=25 (Part A) had reached Week 24 for the snapshot analysis
- No participants met the criteria for resistance analysis

Adherence & Participant-reported Palatability and Acceptability

- All 50 participants reported B/F/TAF as palatable, and with acceptable shape and size (15mm x 8mm)
- Median (Q1, Q3) adherence rate up to the data cut date was 98.8% (97.4%, 100.0%)
  - <80%: 0
  - ≥80% to <90%: 1 (2%)
  - ≥90% to <95%: 5 (10%)
  - ≥95%: 44 (88%)

Conclusions

- In children (aged 6 to <12 years, ≥25kg) living with HIV-1 infection:
- Exposures of BIC, FTC, and TAF were consistent with the ranges of exposures observed in adults in Phase 3 trials of B/F/TAF
- B/F/TAF was well tolerated
- B/F/TAF demonstrated high rates of virologic suppression
- Efficacy and safety were consistent with results from Phase 3 trials of B/F/TAF in adults
- These data suggest B/F/TAF could be a treatment option for children living with HIV and support further investigations of B/F/TAF with age-appropriate formulations in younger children

References

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8. Arribas JR, et al. J Acquir Immune Defic Syndr 2017;75:211-8; 9. Gallant JE, et al. J Acquir Immune Defic Syndr 2017;75:61-6; 10. Gaur A, et al. CROI 2018, #844.

Conflicts of Interest

- Received funding through university for research studies
  - Pharmaceutical: Gilead, ViiV, BMS
  - Vaccine – VPM, PATH, Novavax
  - NIH
  - NIAID: IMPAACT, ACTG
  - NIMH: RO1
  - PENTA-ID
- Served on Speaker's bureau
  - MSD – (World AIDS 2016)
  - ViiV – (Workshop 2016)

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