GILEAD | Medical Information

Biktarvy® (BIC/FTC/TAF) CNS Penetration

This document is in response to your request for information regarding the penetration of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) into the central nervous system (CNS).

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Summary

PK Data on the CNS Penetration of BIC/FTC/TAF

A real-world study assessed the CSF diffusion of BIC/FTC/TAF in 24 participants with HIV-related CNS impairment. Unbound levels of FTC and TFV were undetectable in CSF and plasma. Lower concentrations in the CSF for BIC (total and unbound), FTC, and TFV compared with plasma concentration were reported.[1,2]

An open-label study evaluated the PK of BIC in the CSF of 15 virologically suppressed PWH. BIC concentrations in plasma and CSF of 14 participants were above the EC_{50} of 1.1 ng/mL.[3]

Detectable concentrations of FTC in the CSF were reported in two PK studies of PWH treated with FTC/TDF along with other ARVs.[4,5]

TAF concentrations were undetectable in plasma and CSF at 6 hours after dosing in 9 virologically suppressed PWH who switched from E/C/F/TDF to E/C/F/TAF.[6]

Available CPE scores for the individual components of BIC/FTC/TAF are presented below.

PK Data on the CNS Penetration of BIC/FTC/TAF

Real-World Observational Study

Study design and demographics

An open-label, prospective, single-center, observational study was conducted in France to assess the CSF diffusion of BIC/FTC/TAF in participants with HIV-related CNS impairment. Participants with ≥1 HIV-related CNS impairment and ≥1 month of treatment with optimized ART containing BIC/FTC/TAF were included. Blood and CSF samples were collected during routine care.[1,2]

Table 1. Baseline Demographics and Disease Characteristics (Gele et al)[2]

Key Demographics and Characteristics		BIC/FTC/TAF (N=24)
Age, median (range), years		45 (26–68)
Male/female, n		15/9
CD4 count, median (range), cells/mcL		229 (55–707)
Plasma HIV-RNA >40 c/mL, n (%)		8 (33)
CSF HIV-RNA >40 c/mL, n (%)		2 (8)
HIV-related CNS impairment, %	Progressive multifocal leukoencephalopathy	46
	Cerebral toxoplasmosis	25
	HIV encephalitis	13
	Acute disseminated encephalomyelitis	4
	Cerebral toxoplasmosis with HIV encephalitis	4
	Meningitis associated with primary HIV infection	4
	Varicella-zoster virus meningoencephalitis	4
ART, %	BIC/FTC/TAF	71
	BIC/FTC/TAF + MVC	25
	BIC/FTC/TAF + DRV/r	4
Duration of current ART, median (range), days		33 (27–365)

Abbreviations: DRV/r=ritonavir-boosted darunavir; MVC=maraviroc.

Results

Concentrations of BIC (total and unbound), FTC, and TFV were lower in the CSF than in plasma (Table 2).[2]

Table 2. PK Concentrations of BIC, FTC, and TAF in Plasma and CSF (Gele et al)[2]

PK Parameters, Median (Range)		BIC	FTC	TFV
Plasma concentration	Total, ng/mL	2610 (107–5707)	158 (41–1252)	19.7 (5.7–43.4)
	Unbound, ng/mL	9.3 (0.5–46.9)	Not detected	Not detected
CSF concentration	Total, ng/mL	11.8 (0.5–44.9)	84.4 (28.6–337.4)	1.6 (0.7–4.3)
	Unbound, ng/mL	4.4 (1.6–9.6)	Not detected	Not detected

The median (range) unbound BIC CSF fraction was 34% (15–82%), and the median (range) unbound BIC plasma concentration was 0.33% (0.11–0.92%). The unbound BIC plasma concentration remained stable and did not correlate with the total BIC plasma concentration (P=0.96).[2]

Participants aged >51 years had significantly higher CSF concentrations of the individual components of BIC/FTC/TAF than those aged ≤51 years of age (unbound BIC, P=0.0356; total FTC, P=0.0082; and total TFV, P=0.0413).[2]

Significant correlations were observed between the plasma and CSF concentrations for BIC (r=0.7429; P=0.0002) and FTC (r=0.7654; P<0.0001). The authors noted a limited effect of TAF in the CSF based on low concentrations in the CSF.[1]

Blood-brain barrier damage was reported in 3 participants: 2 had progressive multifocal leukoencephalopathy, and 1 had HIV encephalitis.[1]

PK of BIC in CSF[3]

Study design and demographics

An open-label, single-center study was conducted to evaluate the PK of BIC in the CSF of 15 PWH who were virologically suppressed (Table 3). All participants switched from stable ART to BIC/FTC/TAF. PK parameters were assessed 24 hours after dosing at Week 4.

Table 3. Baseline Demographics and Disease Characteristics (Tiraboschi et al)[3]

Key Demographics and Characteristics	BIC/FTC/TAF (N=15)
Age, median (IQR), years	42 (37–56)
Male, %	86
BMI, median (IQR), kg/m^2	24.7 (23.3–29.7)
CD4 count, median (IQR), cells/mm^3	801 (628–1011)
HIV-1 RNA at diagnosis, median (IQR), c/mL	60,000 (30,094–410,304)
HIV-1 RNA <40 c/mL for >6 months, n (%)	15 (100)
History of AIDS-defining disease, n	4

Results

All participants maintained virologic suppression (HIV-1 RNA <40 c/mL) in plasma and CSF (Table 4). BIC concentrations in plasma and CSF (total and unbound) for 14 of the 15 participants were above the EC_{50} of 1.1 ng/mL. Low concentrations of BIC in plasma (97.9 ng/mL) and CSF (below the lower limit of quantification for both total and unbound) were observed in 1 individual who was taking magnesium supplements. The plasma concentration of BIC increased after magnesium supplements were discontinued.

Table 4. Summary of BIC PK Parameters (Tiraboschi et al)[3]

PK Parameters		BIC (N=15)
Total plasma concentration, median (IQR), ng/mL		1837.1 (1237.2–2586.7)
CSF concentration	Total, median (IQR), ng/mL	6.9 (4.8–10.9)
	Unbound, median (IQR), ng/mL	2.48 (1.6–3.7)
CSF to plasma ratio, median (IQR)		0.003 (0.002–0.004)

Overall, BIC/FTC/TAF was well tolerated, and no significant adverse events were reported.

PK of FTC in the CSF

Two studies that evaluated the PK of FTC in PWH who received FTC/TDF along with other ARVs demonstrated detectable concentrations of FTC in the CSF and suggested a strong association between plasma and CSF FTC concentrations.[4,5] In a study of 30 PWH, plasma FTC concentration was reported as one of the significant predictors of CSF FTC concentration based on a univariate analysis (P<0.0001).[4] In a study of 21 participants, the median (range) FTC concentrations in plasma and CSF were 212 (86.5–445.5) ng/mL and 68 (2.5–98) ng/mL, respectively, with a significant correlation to plasma concentrations (P=0.02) were reported. The FTC CSF-to-plasma ratio (range) was 0.26 (0.05–0.41).[5]

PK of TAF in CSF

Study design

In a single-arm, open-label study, CSF PK and antiviral activity were measured in 9 virologically suppressed PWH who switched from E/C/F/TDF to E/C/F/TAF. Initially, participants continued to take E/C/F/TDF, then switched to E/C/F/TAF at Week 12 and were followed for an additional 12 weeks. Neurocognitive performance was evaluated by the Montreal Cognitive Assessment.[6]

PK results

TFV concentrations declined over time from baseline to Week 24 in both the CSF (3 ng/mL and 0.481 ng/mL; *P*=0.004) and plasma (174 ng/mL and 14.1 ng/mL; *P*=0.004), consistent with the lower effective dose of TAF 10 mg compared with TDF 300 mg.[6,7] Although the switch was associated with reduced TFV concentrations in CSF and plasma, there was an increase in TFV CSF-to-plasma ratio from baseline to Week 24 (1.76% and 3.38%; *P*=0.004).[6]

There was a significant correlation of TFV concentrations in CSF and plasma (*P*<0.0001). At Week 24, median (range) TAF concentrations in plasma peaked 2 hours after dosing at 11.05 (2.84–147.11) ng/mL but were below the lower limit of quantification at 6 hours. TAF was not detected in CSF or plasma at 6 hours.[6]

There were no changes in blood-brain barrier permeability, with a mean CSF-to-serum albumin ratio of 3.86 before switching and 4.86 at Week 24.[6]

Safety

No clinically significant trends in neurocognitive performance or post-dose laboratory abnormalities were observed.[6]

Efficacy

Switching from E/C/F/TDF to E/C/F/TAF maintained virologic suppression in the CSF and plasma. All participants had CSF HIV-1 RNA ≤20 c/mL at Week 24. Eight of 9 participants (89%) had plasma HIV-1 RNA ≤20 c/mL at Week 24. One individual, who had an HIV-1 RNA level of 40 c/mL at Week 24, had a CSF HIV-1 RNA level <20 c/mL.[6]

CPE Score

The CPE ranking system analyzes differences in estimated distribution of ARV drugs into the CNS, with a larger number reflecting estimates of better penetration or effectiveness in the CNS.[8] The relationship between CPE score and neurocognitive or clinical outcomes has not yet been established.[9-11] A CPE score of 3 has been reported for FTC and a score of 1 for TAF.[8,12-14] The CPE score for BIC has not been determined.

References

1. Cheret A, Gele T, Gordon AC, et al. Bictegravir/FTC/TAF CSF Diffusion in HIV-Infected Patients with CNS Impairment [Poster 2327]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 08-11 March, 2020; Boston, MA.

2. Gele T, Cheret A, Castro Gordon A, et al. Cerebrospinal fluid exposure to bictegravir/emtricitabine/tenofovir in HIV-1-infected patients with CNS impairment. *J Antimicrob Chemother.* 2021;76(12):3280-3285.
3. Tiraboschi J, Imaz A, Khoo S, et al. Total and Unbound Bictegravir Concentrations and Viral Suppression in Cerebrospinal Fluid of Human Immunodeficiency Virus-Infected Patients (Spanish HIV/AIDS Research Network, PreEC/RIS 56). *J Infect Dis.* 2020;221(9):1425-1428.
4. Lahiri CD, Reed-Walker K, Sheth AN, Acosta EP, Vunnava A, Ofotokun I. Cerebrospinal fluid concentrations of tenofovir and emtricitabine in the setting of HIV-1 protease inhibitor-based regimens. *J Clin Pharmacol.* 2016;56(4):492-496.
5. Calcagno A, Bonora S, Simiele M, et al. Tenofovir and emtricitabine cerebrospinal fluid-to-plasma ratios correlate to the extent of blood-brain barrier damage. *AIDS.* 2011;25(11):1437-1439.
6. Ma Q, Ocque AJ, Morse GD, et al. Switching to TAF in EVG-Based Regimens: CSF Pharmacokinetics and Antiviral Activity. [Poster 473]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 04-08 March, 2018; Boston, MA.
7. Custodio JM, Ting LS, Zack JZ, et al. Tenofovir Alafenamide Has Wide Efficacious Range for Treatment of HIV-1 Infection: Pharmacokinetic-Pharmacodynamic Relationship From a Phase 3 Study [Poster SUNDAY-407]. Paper presented at: ASM Microbe; 16-20 June, 2016; Boston, MA.
8. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic Complications of HIV Disease and Their Treatment [Author Manuscript]. *Top HIV Med.* 2010;18(2):45-55.
9. Letendre S. Central Nervous System Complications in HIV Disease: HIV-Associated Neurocognitive Disorder. *Topics in antiviral medicine.* 2011;19(4):137-142.
10. Marra CM, Zhao Y, Clifford DB, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS.* 2009;23(11):1359-1366.
11. Carvalhal A, Gill MJ, Letendre SL, et al. Central Nervous System Penetration Effectiveness of Antiretroviral Drugs and Neuropsychological Impairment in the Ontario HIV Treatment Network Cohort Study. *J Neurovirol.* 2016;22:349-357.
12. Eggers C, Arendt G, Hahn K, et al. HIV-1-Associated Neurocognitive Disorder: Epidemiology, Pathogenesis, Diagnosis, and Treatment. *Journal of neurology.* 2017;264:1715-1727.
13. Mukerji SS. HIV in the Brain [Presentation]. Paper presented at: IDWeek; 04-08 October, 2017; San Diego, CA.
14. Santos GMA, Locatelli I, Metral M, et al. Cross-Sectional and Cumulative Longitudinal Central Nervous System Penetration Effectiveness Scores Are Not Associated With Neurocognitive Impairment in a Well Treated Aging Human Immunodeficiency Virus-Positive Population in Switzerland. *Open forum infectious diseases.* 2019;6(7):ofz277.

Abbreviations

ART=antiretroviral therapy
ARV=antiretroviral
BIC=bictegravir
c/mL=copies per mL
CD4=cluster of differentiation 4
CNS=central nervous system
CPE=central nervous system penetration effectiveness
CSF=cerebrospinal fluid
EC_{50}=half-maximal effective concentration
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF=elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
FTC=emtricitabine
PK=pharmacokinetic(s)
PWH=people with HIV
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at: www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.