GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Serology

This document is in response to your request for information regarding Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB) and serology data from phase 3 studies.

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/liver-disease/vemlidy/vemlidy_pi.

Summary

Clinical Data on Serology From Phase 3 Studies With TAF

Studies 108 and 110 compared TAF with TDF in predominantly nucleos(t)ide-naive HBeAg- and HBeAg+ participants with CHB. Participants received double-blind TAF or TDF for 96 to 144 weeks, followed by OL TAF.[1] The following final serology results were reported at Year 8:

- The rates of HBeAg loss and seroconversion were 46% and 31%, respectively, in participants who received TAF only, 44% and 27% in participants who switched to TAF at Week 96, and 46% and 33% in participants who switched to TAF at Week 144.[1]
- The rates of HBsAg loss and seroconversion were ≤5% across all treatment groups, including those who were HBeAg- and HBeAg+.[1,2]

A subanalysis of Studies 108 and 110, which evaluated the PK of TAF to characterize HBeAg+ or HBeAg- participants who achieved HBsAg loss with up to 8 years of treatment, reported the following findings[3]:

- At Year 8, a shorter median time to HBsAg loss was observed in HBeAg+ participants vs HBeAg- participants (126 vs 300 weeks, respectively; *P*=0.02). In HBeAg+ participants, GTs A and F demonstrated the fastest time to HBsAg loss (48 weeks).
- Among HBeAg+ participants, those with the highest baseline HBsAg levels (>100,000 IU/mL) had the highest rates of HBsAg loss relative to those with the lowest levels (<1000 IU/mL); conversely, among HBeAg- participants those with the lowest HBsAg levels at baseline had the highest rates of HBsAg loss.
- Significant factors for HBsAg loss included White race (*P*=0.0026), FibroTest score >0.48 (*P*=0.0078), a ≥1 $\log_{10}$ IU/mL decline in HBsAg at Week 24 (*P*<0.0001), a ≥75% decline in HBsAg at Week 24 (*P*=0.0004), and elevated ALT levels at Week 24 (*P*=0.0221).

Study 4108 compared switching from TDF to TAF vs continuing TDF after ≥1 year of treatment with TDF in virologically suppressed participants with CHB.[4]

- A higher rate of HBsAg loss was observed at Week 48 in participants who continued TDF than in participants who switched to TAF. By Week 96, similar rates of HBsAg loss and seroconversion were observed between the TAF continuation and TDF→TAF groups. Additionally, at Weeks 48 and 96, similar rates of HBeAg loss/seroconversion and similar rates of quantitative HBsAg decline were observed between treatment groups.[4,5]

Clinical Data on Serology From Phase 3 Studies With TAF

Studies 108 and 110

Study designs and demographics

Studies 108 and 110 were phase 3 clinical trials that compared outcomes in predominantly nucleos(t)ide-naive participants with CHB who received once-daily oral administration of TAF 25 mg or TDF 300 mg. A total of 1298 HBeAg- and HBeAg+ adult participants with an HBV DNA level ≥20,000 IU/mL, both with and without compensated cirrhosis, were randomly assigned to receive either double-blind TAF 25 mg or TDF 300 mg for 3 years in Studies 108 (HBeAg-; n=425) and 110 (HBeAg+; n=873).[1] The study allowed participants in both treatment groups to switch to OL TAF at Year 2 or Year 3, and the OL TAF phase was extended to Year 8.[1,2]

The primary endpoint was a non-inferiority margin of 10% in the proportion of participants with undetectable HBV DNA (<29 IU/mL) at Week 48.[6,7]

Table 1. Studies 108 and 110: Baseline Demographics and Disease Characteristics[1,7,8]

Key Demographics and Characteristics	TAF8y (n=866)	TDF2y→OL TAF6y (n=207)	TDF3y→OL TAF5y (n=225)
Age, mean (SD), years	40 (11.8)	42 (12.2)	42 (12.4)
Male, n (%)	544 (63)	126 (61)	149 (66)
Asian, n (%)	687 (79)	167 (81)	166 (74)
ALT, median (Q1, Q3), U/L	80 (56, 123)	81 (53, 136)	79 (51, 121)
Nucleos(t)ide experienced, n (%)	211 (24)	50 (24)	58 (26)
HBV GT, A/B/C/D/other,[a] %	6/19/48/26/1	6/26/45/21/2	8/16/48/28/1
HBV DNA, mean (SD), $\log_{10}$ IU/mL	7 (1.59)	7 (1.66)	7.1 (1.6)
HBeAg+, n (%)	569 (66)	133 (64)	157 (70)
HBsAg, mean (SD), $\log_{10}$ IU/mL	3.8 (0.81)	3.9 (0.76)	3.8 (0.81)
FibroTest score 0.75–1,[b] n/N (%)	76/846 (9)	16/200 (8)	26/221 (12)

[a]Other GTs included E, F, H, and unknown.
[b]Assessed with BioPredictive (Paris, France); FibroTest range is suggestive of cirrhosis (ie, Metavir F4).

Year 8 serology results

Through Year 8, the rates of HBeAg loss and seroconversion were similar among treatment groups during the double-blind phase, and progressively increased during the OL phase.[2] Across treatment groups, HBsAg loss and seroconversion occurred at low rates (≤5%), with small mean declines in levels of HBsAg (Table 2).[1]

Table 2. Studies 108 and 110: Overall Serology Results at Year 8 (M=E Analysis)[1]

Parameter		TAF8y	TDF2y→OL TAF6y	TDF3y→OL TAF5y
HBeAg	Loss, n/N (%)	171/373 (46)	32/73 (44)	50/108 (46)
	Seroconversion, n/N (%)	114/373 (31)	20/73 (27)	36/108 (33)
HBsAg	Loss, n/N (%)	17/583 (3)	4/117 (3)	4/167 (2)
	Seroconversion, n/N (%)	12/583 (2)	4/117 (3)	3/167 (2)
	Change from baseline, mean (SD), log_{10} IU/mL	−0.8 (1.127)	−0.88 (1.219)	−0.93 (1.141)

HBsAg loss and seroconversion and small mean declines in quantitative HBsAg also occurred at low rates (≤5%) through Year 8 in HBeAg- and HBeAg+ participants who were treated with TAF or switched to OL TAF at Year 2 or Year 3 (Table 3).[2]

Table 3. Studies 108 and 110: Serology at Year 8 According to HBeAg- and HBeAg+ Status (M=E Analysis)[1,2]

Parameter		TAF8y		TDF2y→OL TAF6y		TDF3y→OL TAF5y	
		HBeAg- (n=285)	HBeAg+ (n=581)	HBeAg- (n=74)	HBeAg+ (n=133)	HBeAg- (n=66)	HBeAg+ (n=159)
HBeAg	Loss, n/N (%)	N/A	171/373 (46)	N/A	32/73 (44)	N/A	50/108 (46)
	Seroconversion, n/N (%)	N/A	114/373 (31)	N/A	20/73 (27)	N/A	36/108 (33)
HBsAg	Loss, n/N (%)	8/199 (4)	9/384 (2)	0/41	4/76 (5)	1/58 (2)	3/109 (3)
	Seroconversion, n/N (%)	6/199 (3)	6/384 (2)	0/41	4/76 (5)	0/58	3/109 (3)
	Change from baseline, mean (SD), log_{10} IU/mL	-0.62 (0.924)	-0.89 (1.211)	-0.5 (0.526)	-1.09 (1.424)	-0.61 (0.758)	-1.09 (1.268)

At Year 8 in an M=E analysis, rates of viral suppression (HBV DNA <29 IU/mL) were high (94–97%) across treatment groups, regardless of HBeAg status, with 57% to 64% achieving HBV DNA <29 IU/mL with target not detected.[1]

High rates of ALT normalization (AASLD criteria, 78%) were observed among participants treated with TAF for 8 years, regardless of HBeAg status, based on an M=E analysis. ALT normalization rates increased after switching to TAF in participants who were initially randomly assigned to receive TDF (AASLD criteria, 71% and 79%).[1]

A total of 8 participants who received TAF throughout the study discontinued treatment due to HBsAg seroconversion in the double-blind (n=4) and OL phases (n=4), and 4 participants who switched to TAF at Week 96 or Week 144 discontinued due to HBsAg seroconversion during the OL phase.[1]

Safety at Year 8

The incidence of AEs was similar between the TAF and TDF→OL TAF groups in the OL safety analysis, and most AEs were Grade 1 or 2 (Table 4).[1]

Table 4. Studies 108 and 110 OL Safety Analysis: AEs Through Year 8[1]

Safety Outcomes, n (%)	TAF8y (n=775)	TDF→OL TAF[a] (n=382)
Any AE	525 (68)	271 (71)
Treatment-related AEs	43 (6)	18 (5)
Grade ≥3 AE	60 (8)	27 (7)
Grade ≥3 treatment-related AE	2 (<1)[b]	0
SAEs	97 (13)	49 (13)
Serious treatment-related AE	4 (1)[c]	0

Safety Outcomes, n (%)		TAF8y (n=775)	TDF→OL TAF[a] (n=382)
Discontinuation due to AE		9 (1)[d]	3 (<1)[e]
Death		1 (<1)[f]	1 (<1)[g]
HCC[h]		7 (<1)	3 (<1)
AEs that occurred in ≥5% of participants	Headache	59 (8)	30 (8)
	Upper respiratory tract infection	55 (7)	27 (7)
	Nasopharyngitis	52 (7)	23 (6)
	Arthralgia	41 (5)	23 (6)
	Hypertension	37 (5)	26 (7)
	Back pain	34 (4)	23 (6)
	Cough	28 (4)	27 (7)

[a]Included all participants who switched to OL TAF at Year 2 and at Year 3.
[b]Cerebrovascular accident and renal neoplasm (each, n=1).
[c] ALT increase, cerebrovascular accident, osteonecrosis, and renal neoplasm (each, n=1).
[d]Cardiopulmonary failure, cerebrovascular accident, γ-glutamyltransferase increased, HCC, myelodysplastic syndrome, osteonecrosis, osteoporosis, pancreatic carcinoma, and proteinuria (each, n=1).
[e]Tuberculosis, ascites, and pemphigoid (each, n=1).
[f]Pancreatic cancer.
[g]Bilateral pneumonia.
[h]Over the course of the entire study, 21 participants (1.8%) developed HCC (TAF, n=12; TDF→TAF, n=9; *P*=0.33); 10 of these events occurred during the OL phase.

Subanalysis of Studies 108 and 110: TAF PK and HBsAg Loss[3]

Study designs and demographics

A subanalysis of Studies 108 and 110 evaluated the PK of TAF to characterize HBeAg+ or HBeAg- participants who achieved HBsAg loss with up to 8 years of treatment.

Table 5. Subanalysis of Studies 108 and 110: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics		TAF (N=866)		TDF→OL TAF (N=432)	
		HBeAg- (n=285)	HBeAg+ (n=581)	HBeAg- (n=140)	HBeAg+ (n=292)
Age, mean (SD), years		45 (11.6)	38 (11)	48 (10.4)	38 (11.7)
Male, n (%)		173 (61)	371 (64)	86 (61)	189 (65)
Asian, n (%)		205 (72)	482 (83)	101 (72)	232 (80)
Race, n (%)	White	71 (25)	96 (17)	35 (25)	52 (18)
	Black or African American	5 (2)	2 (<1)	3 (2)	3 (1)
ALT, median (Q1, Q3), U/L		67 (44, 102)	85 (61, 139)	67 (47, 102)	86 (57, 137)
Nucleos(t)ide experienced, n (%)		60 (21)	151 (26)	31 (22)	77 (26)
HBV GT, A/B/C/D, %		5/21/40/32	7/17/52/23	4/29/34/30	9/16/52/22
HBV DNA, mean (SD), $\log_{10}$ IU/mL		5.7 (1.34)	7.6 (1.34)	5.8 (1.32)	7.6 (1.41)
HBsAg, mean (SD), $\log_{10}$ IU/mL		3.4 (0.66)	4 (0.79)	3.4 (0.73)	4.1 (0.68)
FibroTest score ≥0.75,[a] n/N (%)		31/280 (11)	45/566 (8)	20/139 (14)	22/282 (8)

[a]Metavir F4/cirrhosis.

Results

At Year 8, in participants who received TAF only or switched to TAF during the OL phase, rates of HBsAg loss were similar: HBeAg-, n/N=10/427 (2%); HBeAg+, n/N=27/873 (3%). The median time to HBsAg loss was significantly shorter in HBeAg+ participants than in HBeAg- participants: 126 vs 300 weeks, respectively (*P*=0.02).

Among HBeAg+ participants, those with the highest baseline HBsAg levels (>100,000 IU/mL) had the highest rates of HBsAg loss; among HBeAg- participants, those with the lowest baseline levels (<1000 IU/mL) had the highest rates of HBsAg loss (Table 6). Regardless of HBV GT, HBsAg loss occurred sooner in HBeAg+ participants than in HBeAg- participants, with GTs A and F demonstrating the fastest time to HBsAg loss (approximately 48 weeks) in the HBeAg+ population.

Table 6. Subanalysis of Studies 108 and 110: HBsAg Loss According to Baseline HBsAg Levels and GT[3]

Rates of HBsAg Loss		TAF	
		HBeAg-	HBeAg+
Baseline HBsAg level, %	<1000 IU/mL	7.2	5.2
	>1000 to <10,000 IU/mL	1.4	0.6
	>10,000 to <100,000 IU/mL	0	3.4
	>100,000 IU/mL	-	9.8
HBV GT, n/N (%)	A	7/64 (11)	2/21 (10)
	B	5/148 (3)	1/100 (1)
	C	6/456 (1)	5/163 (3)
	D	8/197 (4)	2/133 (2)
	E	0/3 (0)	0/7 (0)
	F	2/5 (40)	N/A
	H	N/A	0/2 (0)
	Unknown	N/A	0/1 (0)

Factors significantly associated with HBsAg loss included baseline characteristics such as White race (HR, 2.98; 95% CI:1.46–6.07; *P*=0.0026) and a FibroTest score of >0.48 (HR, 2.6; 95% CI: 1.29–5.25; *P*=0.0078) and treatment factors such as a ≥1 $\log_{10}$ IU/mL decline in HBsAg at Week 24 (HR, 9.4; 95% CI: 4.29–20.62; *P*<0.0001), a decline in HBsAg levels of ≥75% at Week 24 (HR, 12.41; 95% CI: 3.1–49.66; *P*=0.0004), and elevated ALT levels at Week 24 (HR, 2.28; 95% CI: 1.13–4.62; *P*=0.0221).

Serology in Participants Who Switched From TDF to TAF[4,5]

Study design and demographics

Study 4018 was a double-blind, randomized, phase 3 study that evaluated the safety and efficacy of switching from TDF to TAF (n=243) vs continuing TDF (n=245) in virologically suppressed participants with CHB. All participants had been treated with TDF for ≥48 weeks prior to screening, with $eGFR_{CG}$ ≥50 mL/min at screening. At Week 48, all participants were eligible to receive OL TAF and were either switched to TAF from TDF (TDF→TAF) or continued on TAF (TAF→TAF) to Week 96 (Figure 1). The primary endpoint was the number of participants with HBV DNA ≥20 IU/mL (non-inferiority to TDF) at Week 48.

Figure 1. Study 4018: Study Design[4]

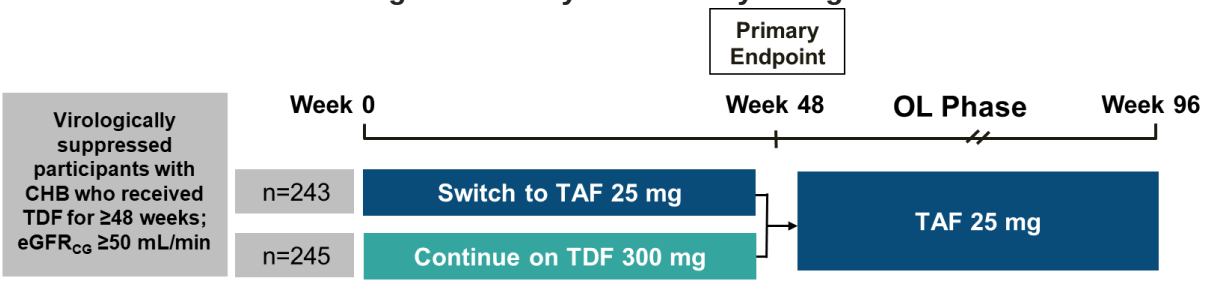

Table 7. Study 4018: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics		TAF (n=243)	TDF (n=245)
Age, median (SD), years		51 (10.5)	51 (10.8)
Age ≥60 years, n (%)		51 (21)	57 (23)
Male, n (%)		179 (74)	166 (68)
Asian, n (%)		195 (80)	205 (84)
HBeAg-, n (%)		165 (68)	166 (68)
ALT, mean (SD), U/L		28 (15.6)	26 (12)
History of cirrhosis, n/N (%)		32/233 (14)	45/235 (19)
$eGFR_{CG}$, median (Q1, Q3), mL/min		91 (77, 110)	90 (76, 109)
Normal bone mineral density status (T-score ≥-1), n (%)	Hip	143 (59)	124 (51)
	Spine	125 (51)	120 (49)

Week 48 and Week 96 serology results

At Week 48, a higher rate of HBsAg loss was observed in participants receiving TDF. By Week 96, similar rates of HBsAg loss and seroconversion were observed between the TAF→TAF and TDF→TAF groups. Additionally, at Weeks 48 and 96, similar rates of HBeAg loss/seroconversion and similar rates of quantitative HBsAg decline were observed between the treatment groups (Table 8).

Table 8. Study 4018: Serology at Week 48 and Week 96[4,5]

Parameter		Week 48			Week 96		
		TAF	TDF	*P*-Value	TAF → TAF	TDF → TAF	*P*-Value
HBeAg	Loss, n/N (%)	6/78 (8)	5/78 (6)	0.73	14/78 (18)	7/78 (9)	0.1
	Seroconversion, n/N (%)	2/78 (3)	0	0.13	4/78 (5)	2/78 (3)	0.42
HBsAg	Loss, n/N (%)	0	5/245 (2)	0.03	4/243 (2)	6/245 (2)	0.54
	Seroconversion, n/N (%)	0	0	-	2/243 (<1)	1/245 (<1)	0.58
	Mean change (SD), log_{10} IU/mL	-0.07 (0.14)	-0.1 (0.29)	0.15	-0.12 (0.28)	-0.13 (0.35)	0.81

Safety

Overall, switching to TAF from TDF was safe and well tolerated, with similar treatment-emergent AEs between treatment groups through Week 96 (Table 9 and Table 10).

Table 9. Study 4018: Safety Through Week 48[4]

Safety Outcomes, n (%)	TAF (n=243)	TDF (n=245)
AE	126 (52)	118 (48)
Grade 3–4 AE	8 (3)	4 (2)
SAE	11 (5)	3 (1)
SAE related to study drug	0	0

Safety Outcomes, n (%)	TAF (n=243)	TDF (n=245)
Discontinued due to AE	2 (<1)	0
HCC	1 (<1)	1 (<1)
Death	0	0

Table 10. Study 4018: Safety From Week 48 Through Week 96[5]

Safety Outcomes, n (%)	TAF→TAF (n=235)	TDF→TAF (n=237)
AE	81 (34)	84 (35)
Grade 3–4 AE	8 (3)	7 (3)
SAE	8 (3)	5 (2)
SAE related to study drug	0	0
Discontinued due to AE	1 (<1)	0
HCC	2 (<1)	1 (<1)
Death	0	0

References

1. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: Final results from two randomised phase 3 trials. *Aliment Pharmacol Ther.* 2024;60(11-12):1573-1586.
2. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: Final results from two randomised phase 3 trials [Supplemental material]. *Aliment Pharmacol Ther.* 2024;60(11-12):1573-1586.
3. Heo J, Fung SK, Buti M, et al. Kinetics of Hepatitis B Surface Antigen Loss Following 8 Years of Tenofovir-Based Treatment in Hepatitis B e Antigen–Negative and Hepatitis B e Antigen–Positive Patients With Chronic Hepatitis B [Presentation 208]. Paper presented at: American Association for the Study of Liver (AASL); November 15–19, 2024; San Diego, CA.
4. Lampertico P, Buti M, Fung S, et al. Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Virologically Suppressed Patients with Chronic Hepatitis B: A Randomised, Double-Blind, Phase 3, Multicentre Non-Inferiority Study. *Lancet Gastroenterol Hepatol.* 2020. https://www.ncbi.nlm.nih.gov/pubmed/32087795
5. Lampertico P, Buti M, Ramji A, et al. A Phase 3 Study Comparing Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide With Continued TDF Treatment in Virologically Suppressed Patients With Chronic Hepatitis B: Final Week 96 Efficacy and Safety Results [Presentation]. Paper presented at: The Digital International Liver Congress; 27-29 August, 2020.
6. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
7. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1(3):185-195.
8. Chan HLY, Buti M, Agarwal K, et al. Maintenance of High Levels of Viral Suppression and Improved Safety Profile of Tenofovir Alafenamide Relative to Tenofovir Disoproxil Fumarate in Chronic Hepatitis B Patients Treated for 5 Years in 2 Ongoing Phase 3 Studies [Poster 803]. Paper presented at: American Association for the Study of Liver Diseases (AASLD): The Liver Meeting Digital Experience; 13-16 November, 2020.

Abbreviations

AASLD=American Association for the Study of Liver Diseases
AE=adverse event
CHB=chronic hepatitis B
CG=Cockcroft-Gault equation
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
M=E=missing=excluded
OL=open-label
PK=pharmacokinetics
Q=quartile
SAE=serious adverse event
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_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.