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Vemlidy® (tenofovir alafenamide) Use in Severe Renal Impairment

This document is in response to your request for information regarding the use of Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of chronic hepatitis B (CHB) in patients with severe renal impairment (RI; eGFR 15–29 mL/min) in patients with end-stage renal disease (ESRD; eGFR <15 mL/min) requiring hemodialysis (HD).

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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

Product Labeling[1]

No dosage adjustment of TAF is required in patients with estimated CrCl ≥15 mL/min, or in patients with ESRD (estimated CrCl <15 mL/min) who are receiving chronic HD. On days of HD, administer TAF after completion of HD treatment.

Postmarketing cases of RI, including acute renal failure, proximal renal tubulopathy, and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to TFV-related AEs.

Patients taking TFV prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating TAF, and during treatment with TAF on a clinically appropriate schedule, assess SCr, estimated CrCl, urine glucose, and urine protein in all patients. In patients with CKD, also assess serum phosphorus. Discontinue TAF in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

TAF is not recommended in patients with ESRD who are not receiving chronic HD, as the safety of TAF has not been established in this population.

Clinical Data on the Use of TAF in Severe RI

In Study 4035, switching to TAF from TDF and/or other OAVs resulted in maintenance of virologic suppression and either stable or improved bone and renal parameters through Week 96 in virally suppressed participants with CHB and moderate to severe RI, including those with ESRD on HD. Efficacy and safety results are summarized below.[2,3]

PK analyses of PWH and participants without HIV who were treated with TAF found that exposures of the renally excreted TFV metabolite were higher in participants with severe RI

and ESRD compared with those in controls. However, TFV AUC was still lower compared to historical TDF-based TFV exposure in participants with normal renal function. Safety results are summarized below.[4,5]

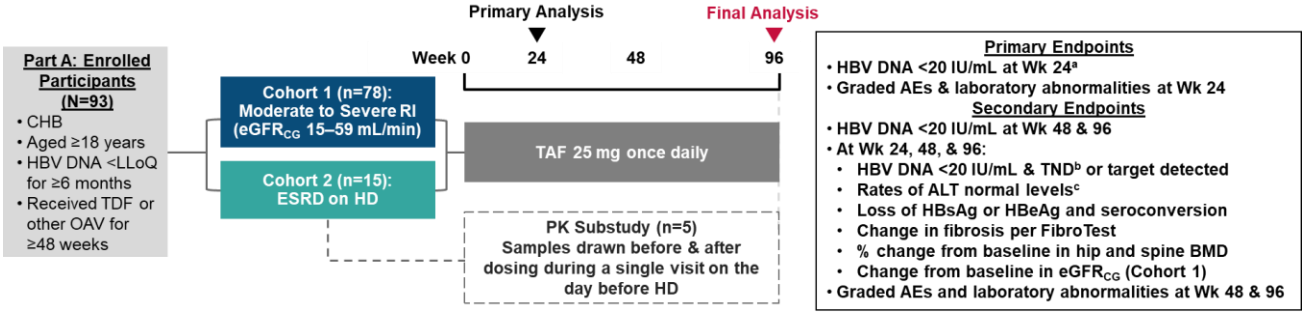
Clinical Data on the Use of TAF in Severe RI

Study 4035: Switching From TDF and/or Other OAVs to TAF in Participants With Renal or Hepatic Impairment

Study design, participant disposition, and demographics[2]

Study 4035 was a phase 2, open-label, 96-week study that evaluated the efficacy and safety of switching from TDF and/or other OAVs to TAF in participants with CHB who were virologically suppressed with moderate to severe RI (Cohort 1, $eGFR_{CG}$ 15 to <60 mL/min; n=78) and in participants with ESRD maintained on HD (Cohort 2, $eGFR_{CG}$ <15 mL/min; n=15; Figure 1). Efficacy endpoints included assessments of virologic suppression (HBV DNA <20 IU/mL; M=F; primary endpoint assessed at Week 24), biochemical response (normal ALT level), and serologic response (HBeAg/HBsAg loss and seroconversion). Safety endpoints included rates of AEs, laboratory abnormalities, changes in fasting lipid levels, and renal and bone parameters. Data from Part A of the study (Cohorts 1 and 2) are summarized below; data from Part B (participants with hepatic impairment) are not summarized.

Figure 1. Study 4035, Part A: Study Design[2]



Abbreviation: LLoQ=lower limit of quantification.
[a]Also evaluated in subgroups according to age (<65 years and ≥65 years) and by male or female gender.
[b]HBV DNA <LLoQ or complete virologic suppression.
[c]ULN ALT levels were ≤25 U/L for females and ≤35 U/L for males (AASLD criteria). Rates of ALT normalization (ie, participants with ALT level >ULN at baseline and later achieved levels ≤ULN) were also measured.
Note: Primary and secondary efficacy endpoints were evaluated via an ITT (M=F) approach. Additional prespecified per-protocol analyses for the primary endpoint, FDA Snapshot analyses (at Weeks 24, 48, and 96), and M=E analyses of virologic suppression and ALT normalization were also performed.

Within Cohort 1, which included participants with moderate-severe RI, 67 participants completed 96 weeks of treatment: 5 participants withdrew consent for further treatment, 3 discontinued treatment due to an AE, 2 stopped the study due to an investigator decision, and 1 died. Within Cohort 2, which included participants with ESRD, 14 participants completed 96 weeks of treatment, and 1 participant died.

Table 1. Study 4035: Baseline Demographics and Disease Characteristics[2,3]

Key Demographics and Characteristics		Cohort 1: Moderate to Severe RI (n=78)	Cohort 2: ESRD on HD (n=15)	Total (N=93)
Age, median (SD), years		66 (10.1)	54 (12.8)	64 (11.4)
Age ≥65 years, n (%)		43 (55)	4 (27)	47 (51)
Male, n (%)		57 (73)	12 (80)	69 (74)
Race, Asian/White/Black/other, %		76/19/4/1	87/0/0/13	77/16/3/3
HBeAg-, n (%)		65 (83)	12 (80)	77 (83)
HBV DNA <20 IU/mL, n (%)		77 (99)	14 (93)	91 (98)
ALT, median (IQR), U/L		19 (13–25)	12 (9–16)	17 (12–24)
ALT ≤ULN (AASLD criteria[a]), n (%)		73 (94)	15 (100)	88 (95)
History of cirrhosis, n (%)		27 (35)	5 (33)	32 (34)
FibroTest ≥0.75,[b] n (%)		11 (14)	0	11 (12)
$eGFR_{CG}$, median (IQR), mL/min		46 (36–55)	7 (6–10)	44 (29–54)
$eGFR_{CKD-EPI}$, median (IQR), mL/min/1.73 m^2		51 (42–60)	5 (4–6)	48 (34–57)
Grade 1/2 dipstick proteinuria, n (%)		33 (42)[c]	N/A	N/A
T-score <-2.5, spine/hip, n (%)		19 (24)/7 (9)	3 (20)/7 (47)	22 (24)/14 (15)
Select comorbid conditions, HTN/hyperlipidemia/DM/CVD, %		58/33/27/18	73/20/13/40	60/31/25/22
Prior OAV treatment,[d] n (%)	TDF	57 (73)	1 (7)	58 (62)
	At screening	56 (72)	1 (7)	57 (61)
	Adefovir	43 (55)	4 (27)	47 (51)
	Lamivudine	42 (54)	4 (27)	46 (49)
	Entecavir	32 (41)	11 (73)	43 (46)
	At screening	18 (23)	10 (67)	28 (30)
	IFN or pegylated IFN	7 (9)	0	7 (8)
	Telbivudine	5 (6)	1 (7)	6 (6)
	Clevudine	2 (3)	0	2 (2)
	Combination of OAVs[e]	2 (3)	0	2 (2)

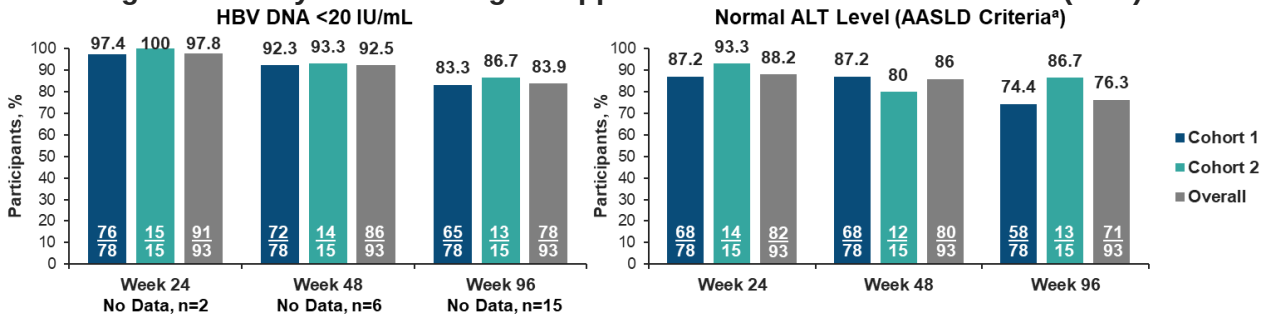
Abbreviations: CKD-EPI=eGFR calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation; CVD=cardiovascular disease; DM=diabetes mellitus; HTN=hypertension; IFN=interferon.
[a]ULN ALT levels were ≤25 U/L for females and ≤35 U/L for males.
[b]FibroTest scores were not available for 1 participant in Cohort 1.
[c]No participants had Grade ≥3 dipstick proteinuria.
[d]Participants could have received treatment with >1 OAV previously.
[e]One participant each previously received adefovir + entecavir and TDF + entecavir in Cohort 1.

Efficacy[2,3]

Virologic suppression rates in Cohort 1 and Cohort 2 were 97.4% and 100%, respectively, at Week 24 (primary endpoint) and decreased to 83.3% and 86.7% at Week 96 (Figure 2). In an M=E analysis, overall (Cohorts 1 and 2 combined) virologic suppression occurred in 100% (91/91), 99% (86/87), and 100% of participants (78/78) at Weeks 24, 48, and 96, respectively. Virologic failure occurred in 1 participant in Cohort 1 at Week 48 per FDA Snapshot Analysis, which was likely due to nonadherence; this participant was later resuppressed at Week 72 and had HBV DNA <20 IU/mL at Week 96. Virologic suppression rates at Week 24 were similar between subgroups according to age and sex (<65 years and ≥65 years; male and female).

At Week 96, normal ALT levels (AASLD criteria) were observed in 74.4% of participants in Cohort 1 and in 86.7% of participants in Cohort 2 (Figure 2). All 5 participants (all in Cohort 1) with ALT levels >ULN at baseline had normalized levels by Week 96 (2 participants at Week 24, 3 at Week 48, and 1 at Week 96).

Figure 2. Study 4035: Virologic Suppression and ALT Normalization (M=F)[2]



[a]Normal ALT levels were ≤25 U/L for females and ≤35 U/L for males at Week 96.

Of the 16 participants who were HBeAg+ at baseline, 1 participant in Cohort 2 experienced HBeAg loss with seroconversion at Week 96, and 1 participant experienced HBsAg loss without seroconversion at Week 48 (Table 2). In a post hoc analysis, the mean decrease in qHBsAg from baseline to each timepoint was small. Of the 11 participants with cirrhosis (FibroTest Metavir F4) at baseline, 9 had Week 96 data; of those participants, 4 had a lower category of fibrosis compared with baseline.

Table 2. Study 4035: Additional Efficacy Endpoints[2,3]

Endpoints	Cohort 1 (n=78)			Cohort 2 (n=15)			Total (N=93)		
	Wk 24	Wk 48	Wk 96	Wk 24	Wk 48	Wk 96	Wk 24	Wk 48	Wk 96
Per protocol: HBV DNA <20 IU/mL	76/76 (100)	NE	NE	14/14 (100)	NE	NE	90/90 (100)	NE	NE
M=E: HBV DNA <20 IU/mL	76/76 (100)	72/73 (98.6)	65/65 (100)	15/15 (100)	14/14 (100)	13/13 (100)	91/91 (100)	86/87 (98.9)	78/78 (100)
HBV DNA TND	59/78 (75.6)	51/78 (65.4)	54/78 (69.2)	9/15 (60)	10/15 (66.7)	10/15 (66.7)	68/93 (73.1)	61/93 (65.6)	64/93 (68.8)
Change in qHBsAg, log_{10} IU/mL	-0.05 (0.12)	-0.06 (0.13)	-0.14 (0.25)	-0.07 (0.12)	-0.1 (0.19)	-0.09 (0.1)	-0.05 (0.12)	-0.06 (0.14)	-0.13 (0.23)
Change in FibroTest score	-0.01 (0.1)	-0.03 (0.1)	-0.01 (0.11)	-0.01 (0.06)	-0.01 (0.07)	0.03 (0.11)	-0.01 (0.09)	-0.02 (0.1)	0 (0.11)

Abbreviation: NE=not evaluated.
Note: Data are presented as n/N (%) or mean (SD).

Safety

Overall, treatment was well tolerated, and the observed AEs, SAEs, and laboratory abnormalities were consistent with those of participants with established renal disease.
No study drug-related Grade 3 to 4 AEs or SAEs were reported. The only study drug-related AE that occurred in ≥2 participants was proteinuria (3%; n=2, both in Cohort 1).
Two participants had AEs that led to treatment interruption: 1 in Cohort 1 due to pneumonia and another in Cohort 2 due to coagulopathy, thrombocytopenia, thrombotic thrombocytopenic purpura, jaundice, and hemoptysis.[2]

Table 3. Study 4035: Week 96 Safety Summary[2]

Safety Outcomes, n (%)		Cohort 1 (n=78)	Cohort 2 (n=15)	Total (N=93)
Any AE		58 (74)	15 (100)	73 (78)
Study drug-related AE		4 (5)	2 (13)	6 (6)
SAE		12 (15)	8 (53)	20 (22)
Grade 3–4 AE		14 (18)	4 (27)	18 (19)
Grade 3–4 AEs in ≥2 participants	Pneumonia	2 (3)	0	2 (2)
	Ischemic stroke	2 (3)	0	2 (2)
	Ovarian cancer	0	2 (13)	2 (2)
	Dyspnea	0	2 (13)	2 (2)
Discontinuation due to AE		3 (4)[a]	0	3 (3)
Interruption in treatment due to AE		1	1	2
Death		2 (3)[b]	1 (7)[c]	3 (3)
Grade 3–4 laboratory abnormalities		13 (17)	11 (73)	24 (26)
Grade 3–4 laboratory abnormalities in ≥2 participants	SCr increased	5 (6)	1 (7)	6 (6)
	Urine glucose	3 (4)	0	3 (4)[d]
	Fasting serum glucose	2 (3)	0	2 (2)
	LDL increased	2 (3)[e]	0	2 (2)[f]
	Hgb decreased	1 (1)	4 (27)	5 (5)
	Amylase increased	1 (1)	3 (20)	4 (4)

[a]Malignant lung neoplasm, respiratory failure, and rectal cancer; none were related to treatment.
[b]Chest infection and respiratory failure on Day 261 and non-traumatic intracerebral hemorrhage on Day 442.
[c]Severe thrombocytopenia on Day 303.
[d]Urine glucose levels were available for 79 participants overall, as only 1 participant in Cohort 2 had data.
[e]LDL levels were available for 76 participants.
[f]LDL levels were available for 91 participants overall.

Renal parameters: Cohort 1

In Cohort 1, $eGFR_{CG}$ and renal laboratory parameters were stable through Week 96 overall and in subgroups according to prior use of TDF or other OAVs (Table 4). Shifts in CKD stage at Week 96 according to baseline CKD stage are shown in Table 5.[2,3]

Table 4. Study 4035, Cohort 1: $eGFR_{CG}$ and SCr Overall and by Prior Use of TDF or Other OAVs Through Week 96[2]

Renal Parameter Levels		Cohort 1		
		All Moderate to Severe RI (n=78)	Prior TDF (n=56)	Other Prior OAVs (n=22)
$eGFR_{CG}$	Baseline, median (IQR), mL/min	45.7 (36.3–54.9)	47.7 (39.1–55.7)	44.3 (36.1–51)
	Change from baseline at Week 96, median, mL/min	+1	+2.5	-2.6
SCr	Baseline, median (IQR), mg/dL	1.36 (1.16–1.6)	1.3 (1.16–1.46)	1.59 (1.29–1.99)
	Change from baseline at Week 96, median, mg/dL	-0.04	-0.06	-0.04

Table 5. Study 4035, Cohort 1: Shifts in CKD Stage From Baseline to Week 96[3]

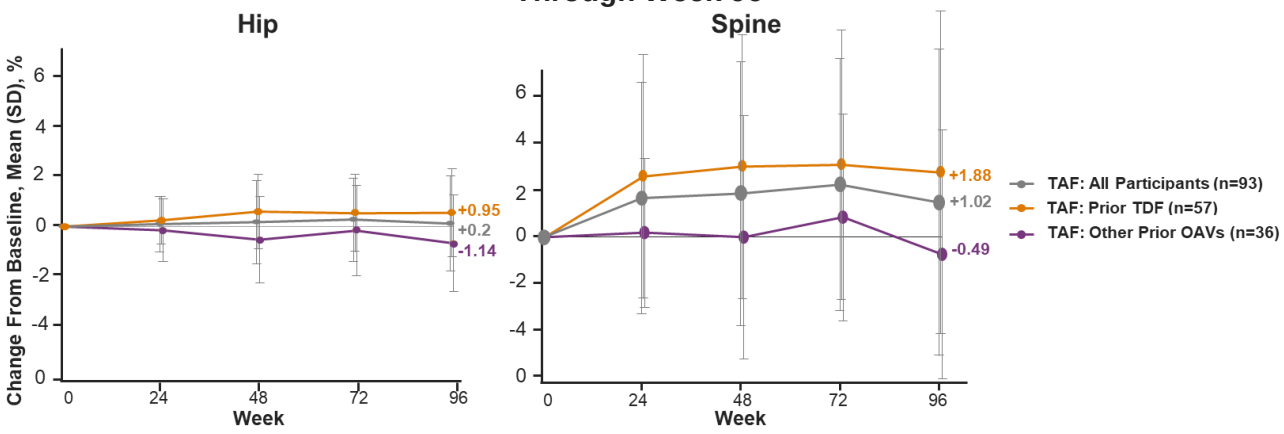
Stage at Week 96, n or n (%)	Baseline CKD Stage						
	Stage 1 (n=0)	Stage 2 (n=6)	Stage 3 (n=63)	Stage 3a (n=37)	Stage 3b (n=26)	Stage 4 (n=9)	Stage 5 (n=0)
Stage 1	0	0	0	0	0	0	0
Stage 2	0	3 (50)	7 (12.3)	7 (21.2)	0	0	0
Stage 3	0	3 (50)	48 (84.2)	N/A	N/A	1 (33.3)	0
Stage 3a	0	3 (50)	N/A	20 (60.6)	4 (16.7)	0	0
Stage 3b	0	0	N/A	6 (18.2)	18 (75)	1 (33.3)	0
Stage 4	0	0	1 (1.8)	0	1 (4.2)	2 (66.7)	0
Stage 5	0	0	1 (1.8)	0	1 (4.2)	0	0
Missing	0	0	6	4	2	6	0

In addition, after treatment was switched to TAF, proximal tubular markers decreased from baseline to Week 96 (median percent change from baseline in RBP:Cr [n=64], -38.5%; in β2M:Cr [n=63], -57%).[3]

Bone parameters[2,3]

Overall, switching to TAF from TDF or other OAVs resulted in stable hip (mean [SD], +0.2% [3.25]) and spine (mean [SD], +1.02% [4.44]) BMD measurements through Week 96 (Figure 3), and percent increases in BMD were observed among those previously treated with TDF relative to those treated with other OAVs. Levels of bone turnover markers (C-type collagen sequence [bone resorption] and procollagen type 1 N-terminal propeptide [bone formation]) decreased but remained relatively stable through Week 96. Two nonserious traumatic bone fractures occurred in Cohort 1; neither was deemed to be treatment related.

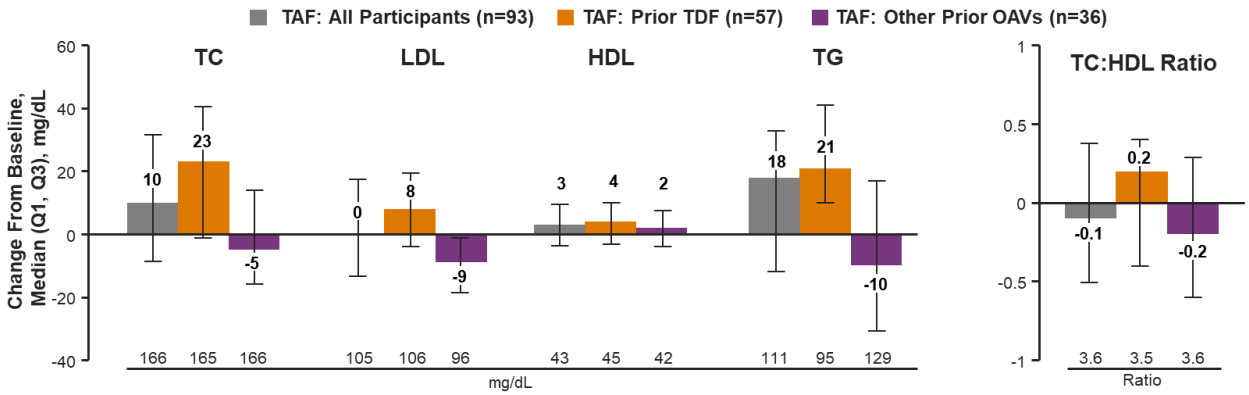
Figure 3. Study 4035: Changes in BMD Overall and by Prior Use of TDF or Other OAVs Through Week 96[2]



Lipid parameters

Small to modest increases in lipid parameters overall were observed at Week 96 after participants switched to TAF, primarily in those who previously used TDF (due to removal of the lipid-lowering effect of TDF); no appreciable changes were seen in TC:HDL ratio (Figure 4). The median (IQR) change from baseline to Week 96 in body weight was +1 (-0.6 to +2.3) kg.[2]

Figure 4. Study 4035: Fasting Lipid Changes Overall and by Prior OAV at Week 96[3]



Abbreviation: TG=triglycerides

PK results[2]

TAF exposures in participants with ESRD on HD were comparable to historical data from PWH. TAF and TFV levels for the 5 participants from Cohort 2 who participated in the PK substudy are presented in Table 6.

Table 6. Study 4035: TAF and TFV PK Parameters for Subgroup of Participants with ESRD on HD in Cohort 2[3]

PK Parameters	Cohort 2 Subgroup (n=5)	
	TAF	TFV
AUC_{τ}, ng·h/mL	307 (20.5)	18,768.7 (30.4)
AUC_{last}, ng·h/mL	295.5 (26.7)	18,768.7 (30.4)
C_{max}, ng/mL	226.2 (48.4)	893.4 (26.4)
T_{max},[a] h	1 (1, 2)	24 (24, 24)
C_{last}, ng/mL	15.7 (144.7)	893.4 (26.4)
T_{last},[a] h	4 (2, 6)	24 (24, 24)
$t_{1/2}$,[a] h	0.44 (0.31, 0.53)	Could not be estimated
CL/F, mL/h	84,568 (24.1)	910.9 (49)

Abbreviations: AUC_{τ}=area under the concentration-time curve over the dosing interval; AUC_{last}=area under the concentration-time curve to the last quantifiable concentration; C_{last}=last quantifiable observation of drug concentration; C_{max}=maximum concentration; CL/F=apparent oral clearance of drug; $t_{1/2}$=terminal elimination half-life; T_{last}=time that the last quantifiable drug concentration was observed; T_{max}=time to maximum concentration.
[a]Data are presented as median (Q1, Q3).

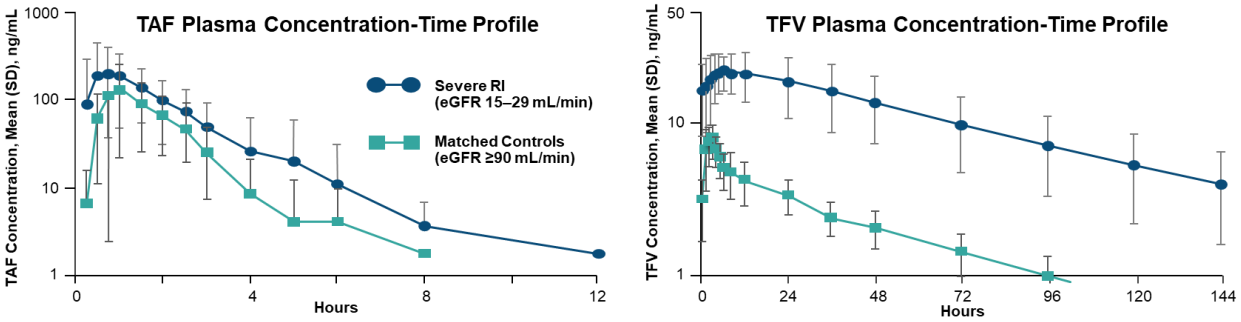
Phase 1, Open-Label, Single-Dose Study[4,5]

The PK of TAF and its metabolite, TFV, were evaluated in participants without HIV and with severe RI (eGFR 15–29 mL/min) and were matched with healthy volunteers (eGFR ≥90 mL/min) in a phase 1, open-label, single-dose study. Twenty-seven participants were enrolled (severe RI, n=14; healthy volunteers, n=13), and each received a single dose of TAF 25 mg. Blood and urine samples for TAF and TFV PK analyses were collected over 7 days after the TAF dose, and participants were followed for 14 days.

The AUC_{inf} for TAF and TFV were 92% and 470% higher, respectively, in participants with severe RI than in healthy volunteers. However, a 25-mg TAF dose in participants with severe RI resulted in 10% to 40% lower TFV AUC values (AUC_{inf}, 2070 h·ng/mL) compared

with historical TDF-based TFV exposures in participants with normal renal function (AUC_{inf}, 2730 h·ng/mL).

Figure 5. TAF and TFV PK Following a Single Dose of TAF 25 mg (Custodio et al)[4]



The overall incidence of AEs was comparable between participants with severe RI and healthy volunteers. All treatment-emergent AEs were determined to be Grade 1 in severity. No clinically relevant changes in the median SCr level, eGFR, or phosphate level were observed in any participant in either group. There were no discontinuations due to AEs.

References

1. Enclosed. Gilead Sciences Inc, VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Janssen HLA, Lim YS, Lampertico P, et al. Switching to tenofovir alafenamide in patients with virologically suppressed chronic hepatitis B and renal or hepatic impairment: final week 96 results from an open-label, multicentre, phase 2 study. *Lancet Gastroenterol Hepatol.* 2024;9(8):718-733.
3. Janssen HLA, Lim YS, Lampertico P, et al. Switching to tenofovir alafenamide in patients with virologically suppressed chronic hepatitis B and renal or hepatic impairment: final week 96 results from an open-label, multicentre, phase 2 study. [Supplementary appendix 1]. *Lancet Gastroenterol Hepatol.* 2024;9(8):718-733.
4. Custodio JM, Fordyce M, Garner W, et al. Pharmacokinetics and Safety of Tenofovir Alafenamide in HIV-Uninfected Subjects with Severe Renal Impairment. *Antimicrob Agents Chemother.* 2016;60(9):5135-5140. http://www.ncbi.nlm.nih.gov/pubmed/27216057
5. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clinical Pharmacokinetics.* 2004;43(9):595-612.

Abbreviations

β2M:Cr=β2-microglobulin to Cr ratio
AASLD=American Association for the Study of Liver Diseases
AE=adverse event
AUC=area under the concentration-time curve
AUC_{inf}=area under the concentration-time curve extrapolated to infinity
BMD=bone mineral density
CG=Cockcroft-Gault
CHB=chronic hepatitis B
CKD=chronic kidney disease
ESRD=end-stage renal disease
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HD=hemodialysis
M=E=missing=excluded
M=F=missing=failure
OAV=oral antiviral
PK=pharmacokinetic(s)
PWH=people with HIV
Q=quartile
qHBsAg=quantitative hepatitis B surface antigen
RBP:Cr=retinol-binding protein to Cr ratio
RI=renal impairment
SAE=serious adverse event
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TND=target not detected

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:

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