A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- During development, small, reversible increases in serum creatinine have been observed in clinical trials. These changes are consistent with *in vitro* data indicating that dolutegravir (DTG; S/GSK1349572) is an inhibitor of organic cation transporter 2 (OCT2).
- Similar to other agents such as trimethoprim and cimetidine, this pattern of rapid onset and small mean increases in creatinine without progression is typical of blockade of creatinine secretion via OCT2.
- This study intends to characterize the mechanism behind the increase in serum creatinine observed during DTG therapy, specifically addressing whether there is any effect on glomerular filtration.

WHAT THIS STUDY ADDS

- The results of the study support *in vitro* data that show DTG is a potent inhibitor of human OCT2 at clinically relevant concentrations and that DTG 50 mg once daily and twice daily had no effect on glomerular filtration rate compared with placebo.
- These data further demonstrate that the reversible increases in creatinine observed in DTG clinical studies are due to the non-pathologic inhibition of OCT2 in the proximal renal tubules and represent a benign effect on renal handling of creatinine.

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AIM

Dolutegravir (DTG; S/GSK1349572) is under clinical development as a once daily, unboosted integrase inhibitor for the treatment of HIV infection. The effect of DTG on glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and creatinine clearance (CL_{cr}) was evaluated in 34 healthy volunteers.

METHODS

Subjects received DTG 50 mg (once daily or twice daily) or placebo for 14 days. GFR was measured by iohexol plasma clearance, ERPF was assessed by para-aminohippurate plasma clearance and CL_{cr} was measured by 24 h urine collection.

RESULTS

All treatments were generally well tolerated. A modest decrease (10–14%) in CL_{cr} was observed, consistent with clinical study observations. DTG 50 mg once daily and twice daily had no significant effect on GFR or ERPF compared with placebo over 14 days in healthy subjects.

CONCLUSIONS

These findings support *in vitro* data that DTG increases serum creatinine by the benign inhibition of the organic cation transporter 2, which is responsible for tubular secretion of creatinine.

Introduction

Creatinine is a catabolic by-product of creatine breakdown in the skeletal muscle tissue and is eliminated almost entirely in the urine. Elimination of creatinine is freely filtered by the glomerulus and is not reabsorbed nor metabolized by the kidney [1, 2]. However, within the renal tubules, creatinine undergoes active secretion via the action of several transporters, including the organic cation transporter (OCT) family. OCT2 is the predominant transporter regulating creatinine secretion along the basolateral surface of the proximal tubules in the kidneys [2, 3].

Dolutegravir is rapidly absorbed after oral administration and has a terminal half-life of approximately 14 h. It is metabolized primarily by hepatic UGT1A1 with a minor role of CYP3A. Renal elimination of unchanged DTG is very low (<1% of the dose) [4]. Small mean increases in serum creatinine have been observed in studies of both healthy volunteers and subjects with HIV infection treated with DTG. These small changes in serum creatinine (mean, 0.1 mg dL⁻¹) generally appear within a week of treatment initiation, plateau and then trend back towards the baseline concentrations while on DTG treatment [5, 6]. The magnitude of change and its pattern (rapid onset and without progression) is typical of blockade of creatinine secretion via OCT2 and has been observed with other agents such as trimethoprim and cimetidine [7, 8]. As such, *in vitro* studies have confirmed that DTG is a potent inhibitor of human OCT2 at clinically relevant concentrations [9]. The objective of this study was to characterize further the mechanism behind the increase in serum creatinine observed during DTG therapy and specifically to determine whether DTG has any effect on glomerular filtration rate (GFR); as measured by iothexol (Omnipaque™; GE Healthcare, Mississauga, ON, Canada), which is freely filtered at the glomerulus but not secreted or reabsorbed within the renal tubules or effective renal plasma flow (ERPF); as measured by para-aminohippurate (PAH).

Methods

Study design

This was an open-label, randomized, three-arm, parallel, placebo-controlled study in 34 healthy adult subjects. Healthy males or females between 18 and 65 years of age with normal renal function (defined as creatinine clearance [CL_{cr}] ≥ 80 mL min⁻¹ 1.73 m⁻² as measured by 24 h urine collection) were included. Subjects with any preexisting condition that interfered with normal gastrointestinal anatomy or motility and those with hepatic and/or renal dysfunction, including a history of nephrolithiasis, were excluded. Subjects were also excluded if they had evidence of microalbuminuria (defined as albumin : creatinine ratio in a random spot urine ≥ 30 mg g⁻¹) at screening. Use of concomitant medications, including antacids, vitamins and

iron supplements, were prohibited. Subjects were assigned to one of the two treatment groups or the placebo group in accordance with the randomization schedule generated by Discovery Biometrics prior to the start of the study using validated internal software.

This study was conducted in accordance with Good Clinical Practice and all applicable regulatory requirements, including the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from each subject, and the study was approved by the Western Institutional Review Board (Olympia, WA, USA).

Study treatment

A screening visit occurred within the 30 days before the first dose of study drug and subjects returned to the clinic 2 days before their first dose of study medication. They remained in the unit upon arrival for the duration of the 14 day trial. In one treatment arm, all subjects received DTG 50 mg (given as two 25 mg tablets) once daily on days 1 through 14. In the second treatment arm, subjects received DTG 50 mg twice daily on days 1 through 14. In the third arm, subjects received a placebo tablet once daily for 14 days. Subjects also received iothexol and PAH infusions on days -1, 7 and 14. There was a follow-up visit 7 to 10 days after the last dose of study medication.

Pharmacodynamic assessment

Each subject was administered a 5 mL dose of iothexol (647 mg mL⁻¹), which was injected slowly over 5 min at baseline (on the morning of day -1) and then immediately after study drug on days 7 and 14. Plasma samples of iothexol were collected pre-dose and 0.5, 1, 1.5, 2, 3, 4 and 5 h after the start of each iothexol dose. All subjects were required to maintain a water intake daily of more than 1000 mL while enrolled in the study. Included with the iothexol dose, 2 g / 10 mL (20%) of PAH at 8 mg kg⁻¹ was mixed into the same syringe and administered to each subject. A continuous infusion of PAH at 12 mg min⁻¹ over approximately 3 h followed the completion of the bolus dose on days -1, 7 and 14. PAH clearance was measured at 30, 90, 150 and 180 min after the start of the PAH loading dose for each visit. Plasma samples were analyzed for both iothexol and PAH concentrations using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with tandem mass spectroscopy (HPLC-MS/MS) analysis. The lower limit of quantification was 1 µg mL⁻¹ and a higher limit of quantification was 100 µg mL⁻¹.

Urine samples for the 24 h CL_{cr}, albumin, total protein and other exploratory renal biomarkers of tubular injury (β₂-microglobulin, N-acetyl-B-glucosaminidase [NAG] and retinol-binding protein) were obtained in conjunction with collection of iothexol and PAH clearance on days -1, 7, and 14. Cystatin C, an additional biomarker of GFR, was also collected. A complete blood count and serum chemistries, including serum creatinine, were collected at screening

and predose on days 1, 7 and 14. Serum creatinine measurements were also collected on days –1, 4 and 10.

Iohexol plasma clearance, PAH plasma clearance, and CL_{cr} were calculated for days –1, 7 and 14. Iohexol plasma clearance (in $ml\ min^{-1}$) was calculated as dose divided by area under the plasma concentration–time curve from 0 to infinity ($AUC(0,\infty)$). PAH plasma clearance (in $ml\ min^{-1}$), as a measure of ERPF, was calculated as $(12\ mg\ min^{-1}) \times (1000/S)$, where $12\ mg\ min^{-1}$ was the infusion rate of PAH used and S was the average steady-state plasma concentration (in $\mu g\ ml^{-1}$) of PAH at 30 (if data show steady-state is achieved), 90 (if data show steady-state is achieved), 150 (if data show steady-state is achieved) and 180 min after the start of intravenous infusion. Creatinine clearance (in $ml\ min^{-1}$) was estimated by $(Ae(0,24\ h) \times 100)/(Cr_s \times 1440\ min)$, where $Ae(0,24\ h)$ is total amount of creatinine excreted in the urine during a 24 h collection interval (in $mg\ 24\ h^{-1}$) and Cr_s is the serum creatinine concentration (in $mg\ dl^{-1}$) observed during the same 24 h interval (the 12 h post-dose sample). Body surface area–normalized values (in $ml\ min^{-1}\ 1.73\ m^{-2}$) for iohexol plasma clearance, PAH plasma clearance and CL_{cr} were also calculated.

Pharmacokinetic assessment

Blood samples for plasma DTG pharmacokinetic (PK) assessment were collected at pre-dose and 1, 2, 3, 4, 6, 8, 12 and 24 h (for 50 mg once daily dose only) after the morning dose on day 14. Human plasma samples were analyzed for DTG using a validated analytical method based on protein precipitation, followed by HPLC-MS/MS analysis. The lower limit of quantification for DTG was $20\ ng\ ml^{-1}$ using a $25\ \mu l$ aliquot of human plasma with a higher limit of quantification of $20\ 000\ ng\ ml^{-1}$.

For subjects in each active treatment group, the following PK parameters were determined from the plasma concentration–time data for DTG: area under the plasma concentration–time curve from 0 to the end of the dosing interval ($AUC(0,\tau)$), area under the plasma concentration–time curve from 0 to 24 h ($AUC(0,24\ h)$), $AUC(0,24\ h)$ for the 12 h dosing was calculated by doubling the $AUC(0,12\ h)$, maximum observed drug concentration (C_{max}), concentration at the start of the dosing interval (C_0) and concentration at the end of the dosing interval (C_τ).

The PK parameters were calculated by standard non-compartmental analysis using WinNonlin® Professional Edition v5.2 or higher (Pharsight®, St Louis, MO, USA). Actual sampling time from dosing was used in the derivation of all PK parameters. DTG PK parameters were summarized by DTG treatment.

Statistical analysis

The sample size of 12 (in order to obtain 10 evaluable subjects) per arm was chosen based on expected withdrawal rate of approximately 20% and a within-subject variability of about 9% for iohexol plasma clearance. This

sample was selected to provide at least 92% power such that the lower bound of the confidence interval (CI) for the ratio (geometric mean; day 14 : day –1 for iohexol plasma clearance) would exceed 0.80 assuming an underlying true ratio of ≥ 0.95 [10].

Body surface area–normalized iohexol plasma clearance, PAH plasma clearance, and CL_{cr} were analyzed for the primary comparisons between day –1 (without DTG or placebo) and day 14 (with DTG or placebo) by a linear mixed effect repeated measures analysis of variance model for log-transformed data. The model included treatment, day and treatment-by-day interactions as fixed effect and subject as a random effect. The comparisons were also adjusted by placebo group (the day 14 : day –1 ratio for DTG groups was compared with the day 14 : day –1 ratio for the placebo group). Geometric mean ratios and corresponding 90% CIs for placebo-adjusted day 14 vs. day –1 comparison were calculated. To conclude no difference before and after treatments, 90% CIs of the geometric mean ratios need to fall entirely within the range of 0.8–1.25. Comparisons were also made between the iohexol plasma clearances (in $ml\ min^{-1}\ 1.73\ m^{-2}$) at day –1 (reference) and at day 7 (test).

The changes from baseline for the exploratory renal biomarkers were summarized descriptively. To explore the relationship between pharmacodynamic endpoints (iohexol plasma clearance, PAH clearance, CL_{cr} , cystatin C, β_2 -microglobulin, NAG and retinol-binding protein) and DTG PK parameters, changes from baseline at days 7 and 14 were plotted against PK parameters (results not presented), and Pearson correlation and P value between these endpoints and the PK parameters were determined.

Results

Subject demographics and study treatment

A total of 38 subjects with an overall mean age of 31.8 years (SD 11.60) were enrolled in the study and received study treatment (Table 1). The majority of the subjects were male (74%) and White (78%). The treatment groups were balanced with regard to demographic characteristics.

Of the 38 subjects enrolled, 34 subjects (89%) completed the study as planned. Three subjects withdrew consent, including one subject who withdrew consent on day –1 after the dose of iohexol and PAH but did not receive a dose of study medication. The other two subjects were replaced. One subject was withdrawn due to an adverse event (AE; loss of appetite and nausea).

Pharmacodynamics

Summary of body surface area–normalized iohexol plasma clearance, PAH plasma clearance, and CL_{cr} by treatment and day are provided in Table 2. When comparing day 14 and day –1 response after adjusting for placebo (Table 3), the geometric mean ratios (90% CI) for iohexol plasma

Table 1

Summary of subject demographic characteristics

Demographics	DTG 50 mg once daily <i>n</i> = 12	DTG 50 mg twice daily <i>n</i> = 13*	Placebo once daily <i>n</i> = 12
Age, mean (SD), (years)	26.8 (8.86)	30.2 (11.60)	38.8 (11.92)
Gender, <i>n</i> (%)			
Female	4 (33%)	3 (23%)	3 (25%)
Male	8 (67%)	10 (77%)	9 (75%)
BMI, mean (SD), (kg m ⁻²)	26.31 (3.050)	24.80 (2.885)	26.34 (2.846)
Height, mean (SD), (cm)	174.11 (10.445)	180.53 (8.185)	173.89 (5.544)
Weight, mean (SD), (kg)	79.87 (12.294)	81.00 (11.986)	79.84 (10.865)
Ethnicity, <i>n</i> (%)			
Hispanic or Latino	1 (8%)	0	0
Not Hispanic or Latino	11 (92%)	13 (100%)	12 (100%)
Race, <i>n</i> (%)	<i>n</i> = 11	<i>n</i> = 13	<i>n</i> = 12
African American/African heritage	2 (18%)	2 (15%)	1 (8%)
Asian (East Asian heritage)	0	0	1 (8%)
Asian (Central/South Asian heritage)	1 (9%)	0	0
White (White/Caucasian/European heritage)	8 (73%)	11 (85%)	9 (75%)
Mixed race	0	0	1 (8%)

BMI, body mass index; DTG, dolutegravir; PAH, para-aminohippurate; *One subject withdrew consent on the evening of day -1, after the first dose of iohexol and PAH. Subject was randomized but did not receive either study medication.

Table 2Body surface area-normalized iohexol plasma clearance, PAH clearance, and creatinine clearance (ml min⁻¹ 1.73 m⁻²) by treatment and day*

Treatment	Day	Iohexol clearance	PAH clearance	Creatinine clearance
DTG 50 mg once daily	-1	120 (23)	583 (16)	116 (17)
	7	121 (20)	606 (19)	102 (27)
	14	106 (15)	582 (17)	106 (21)
DTG 50 mg twice daily	-1	118 (18)	577 (20)	113 (15)
	7	118 (17)	626 (29)	114 (14)
	14	107 (13)	539 (14)	98.7 (12)
Placebo once daily	-1	123 (6)	544 (16)	109 (18)
	7	122 (16)	620 (16)	119 (13)
	14	107 (15)	525 (19)	110 (12)

CV, coefficient of variance; DTG, dolutegravir; PAH, para-aminohippurate; *Geometric mean (CV%).

Table 3

Placebo-adjusted comparison between day 14 and day -1 body surface area-normalized iohexol clearance, PAH clearance and creatinine clearance*

	Iohexol clearance	PAH clearance	Creatinine clearance
Day 14/Day -1 DTG 50 mg once daily to day 14/day -1 placebo	0.993 (0.915, 1.078)	1.029 (0.921, 1.150)	0.900 (0.808, 1.002)
Day 14/Day -1 DTG 50 mg twice daily to day 14/day -1 placebo	1.045 (0.963, 1.135)	0.969 (0.866, 1.083)	0.861 (0.772, 0.960)

DTG, dolutegravir; PAH, para-aminohippurate; *Data presented are geometric mean ratio (90% confidence interval).

clearance were 0.993 (0.915, 1.0780) for DTG 50 mg once daily and 1.045 (0.963, 1.135) for DTG 50 mg twice daily. Similar findings were also obtained when comparing the day 7 and day -1 ratio. The CIs of the day 14 and day -1 ratio corrected for placebo includes 1, with the lower bounds both greater than 0.87 confirming that there was

no change in iohexol plasma clearance at day 14 with DTG treatment. An analysis of PAH clearance showed no change in renal plasma flow with DTG, with the geometric mean ratio (90% CI) for day 14: day -1 PAH plasma clearance estimated at 1.03 (0.921, 1.15) for DTG once daily and 0.969 (0.886, 1.08) for DTG twice daily, respectively. As expected,

Table 4

Summary of plasma DTG pharmacokinetic parameters following repeated dose administration*

Treatment	n	AUC(0,τ) (μg ml ⁻¹ h)	AUC(0,24 h) (μg ml ⁻¹ h)	C _{max} (μg ml ⁻¹)	C ₀ (μg ml ⁻¹)	C _t (μg ml ⁻¹)
DTG 50 mg once daily	11	39.1 (38)	39.1 (38)	2.83 (27)	0.91 (142)	0.84 (61)
DTG 50 mg twice daily	11	51.6 (36)	103 (36)	5.50 (34)	4.18 (44)	3.02 (40)

AUC(0,24 h), area under the plasma concentration–time curve from 0 to 24 h; AUC(0,τ), area under the plasma concentration–time curve from 0 to the end of the dosing interval; C_{max}, maximum observed drug concentration; C₀, concentration at the start of the dosing interval; C_t, concentration at the end of the dosing interval; CV, coefficient of variation; DTG, dolutegravir; *Geometric mean (CV%).

DTG decreased 24 h CL_{cr} by 10% at 50 mg once daily and 14% at 50 mg twice daily after 14 days of dosing.

Pharmacokinetics

The summary of the PK parameters for DTG are presented in Table 4. The AUC(0,24 h) was greater than dose proportional between the once daily and twice daily dosing treatments. Intersubject variability was low to moderate, ranging from 27–34% for C_{max} and 40–61% for C_t.

Exploratory markers of kidney function

None of the exploratory markers (serum cystatin C, along with urinary β₂-microglobulin, NAG and retinol-binding protein) was significantly correlated with DTG PK parameters. Furthermore, no significant changes were observed between DTG groups and placebo in change from baseline for any of these markers (data not shown).

Pharmacokinetic-pharmacodynamic relationship

The Pearson analysis showed that there was no correlation between DTG PK parameters (AUC(0,24 h), C_{max} and C_t) and change from baseline in pharmacodynamic endpoints, including iothexol plasma clearance, PAH plasma clearance, CL_{cr}, cystatin C, β₂-microglobulin, NAG and retinol-binding protein.

Safety

DTG 50 mg once daily and twice daily was generally well tolerated in healthy subjects in this study. No serious AEs were reported. One subject was withdrawn due to the mild to moderate AEs of loss of appetite and nausea, which were considered by the investigator to be possibly related to study drug.

Similar proportions of subjects in the DTG and placebo groups had AEs overall. The most common AEs were conjunctival hyperaemia (two subjects; 5%) and decreased appetite (two subjects; 5%). All other AEs were reported in one subject each. No grade 3 or 4 AEs were reported during this study. The most common drug-related AE was decreased appetite (two subjects in the twice daily group; one grade 1 and one grade 2 AE). All other drug-related AEs were reported in one subject each.

No clinically significant trends or values were reported for vital signs and electrocardiograms. Mean serum creatinine was 0.88, 0.96, and 0.93 mg dl⁻¹ on day –1 and 0.96, 1.12, and 0.90 mg dl⁻¹ on day 14 in the 50 mg once daily, 50 mg twice daily and placebo groups, respectively. Otherwise, there were no differences in haematology or clinical chemistry values between active treatments and placebo, including assessments of blood urea nitrogen, potassium and bicarbonate.

Two subjects receiving placebo had grade 2 proteinuria (defined as a dipstick measure of 2+ proteinuria) at the follow-up visit. Two additional subjects had grade 1 proteinuria (defined as a dipstick measure of >1+) at follow-up as well, one in the 50 mg twice daily group and one in the placebo group. Upon re-examination immediately after the follow-up visit, the subjects had no evidence of proteinuria via dipstick assay. The protein : creatinine ratio for each subject was also obtained at days –1, 7, and 14 and at follow-up with no occurrences of proteinuria in the DTG or placebo groups at any of the time points, including the subjects with proteinuria noted by dipstick (data not shown). No other significant changes in urine protein were observed during the study.

Discussion

This study demonstrated that administration of DTG decreased serum CL_{cr} by 10–14% but had no effect on GFR (as measured by iothexol plasma clearance). DTG also had no effect on ERPF (as measured by PAH plasma clearance). The study provides further support for the hypothesis that the small, reversible increases in serum creatinine observed in clinical studies are due to the inhibition of the tubular secretion of creatinine via OCT2 and does not represent a nephrotoxic effect.

In a dose ranging study of DTG, a non-progressive mean increase from baseline in creatinine of approximately 0.1 mg dl⁻¹ (SD 0.108) was observed across all doses. The creatinine values increased at week 1 and remained constant until about week 16, followed by a gradual return toward baseline over 48 weeks. A similar increase was not observed in the efavirenz (Sustiva®; Bristol-Myers Squibb Company, Princeton, NJ, USA) control

group [6]. The changes in serum creatinine during DTG treatment are consistent with the blockade of the tubular secretion of creatinine. We explored whether DTG inhibited the renal transport protein OCT2 like cimetidine (Tagamet®; GlaxoSmithKline, Moon Township, PA, USA) and trimethoprim [7, 8]. This hypothesis is supported by *in vitro* data that demonstrated that cimetidine inhibited OCT2 with an estimated inhibitory concentration at 50% (IC₅₀) of 189 µM, while DTG inhibited OCT2 with an estimated IC₅₀ of 1.93 µM [9].

For drugs such as cimetidine, OCT2-mediated effect on serum creatinine does not represent a decrease in renal function as measured by a decrease in GFR. The clearance of biomarkers, such as the freely filtered compound iothexol, can aid in establishing the true effect of drugs on the patient's actual GFR. Iothexol total plasma clearance, calculated from consistent, timed measurements of the plasma concentrations following a single infusion, has been shown to equal an individual's GFR. Thus, unlike serum creatinine concentrations, which may be influenced by agents that inhibit active renal tubular excretion, iothexol is freely filtered and is neither secreted nor reabsorbed in the renal tubules, and therefore is a more accurate measure of a patient's true GFR [11, 12].

DTG doses selected for this study are those currently being investigated in ongoing trials. DTG 50 mg once daily is the clinical dose for integrase inhibitor-naïve patients and DTG 50 mg twice daily is the dose being evaluated in subjects with documented resistance to raltegravir (Isentress®; Merck & Co, Inc, Whitehouse Station, NJ, USA). The study duration of 14 days was selected given that serum creatinine concentrations peak around the second week of dosing with DTG [5, 6]. Though our study cannot rule out an effect of longer term dosing on renal function, the return of serum creatinine towards baseline over time is not consistent with nephrotoxicity.

In our study, three subjects in the placebo group and one in the DTG 50 mg twice daily group had proteinuria from a dipstick assay at follow-up but no proteinuria by measurement of protein : creatinine ratio. It is possible for a dipstick urinalysis to be falsely positive in urine with a high specific gravity, urine that is alkaline or urine with haematuria [13]. The gold standard for measuring proteinuria in the urine is the protein : creatinine ratio and is currently recommended by the National Kidney Foundation-K/DOQI guidelines. It provides a more quantitative and accurate assessment of the true amount (if any) of protein in the urine [14]. During our study, no occurrences of proteinuria at any time point, including follow-up, were found with respect to the protein : creatinine ratio in any of the subjects enrolled. While three of the four subjects in the placebo group and one subject in the DTG group experienced grade 1 or grade 2 proteinuria based on dipstick, this was not documented by protein : creatinine ratio, and each subject had normal protein dipstick evaluation upon re-examination shortly after follow-up. Other markers, such

as β_2 -microglobulin, NAG and retinol-binding protein, were also used to provide a complete assessment. No significant changes were observed between the DTG and placebo groups in their change from baseline for any of these markers.

In conclusion, DTG 50 mg once daily and twice daily had no effect on GFR compared with placebo over 14 days. These data further demonstrate that the reversible increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of OCT2 in the proximal renal tubules and represent a benign effect on renal handling of creatinine.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare JK, JB, SC, IS, AP, TK, CC, HM and SCP had support from Shionogi-ViiV Healthcare LLC for the submitted work. JK is an employee of ViiV Healthcare, JB, SC, IS, AP and SCP are employees of GlaxoSmithKline, TK was an employee of Shionogi & Co., Ltd while contributing to this study and manuscript and currently is at Fukushima Prefectural Medical School, Fukushima City, Japan CC and HM are employees of DaVita Clinical Research.

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Author contributions

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

JK, JB, SC, IS, AP, TK, and SCP designed the study. CC and HM conducted the study. All authors contributed to the data analyses. The report was drafted by JK. All authors reviewed the report and have seen and approved the final version.

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