

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211284Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY (OCP) ADDENDUM

NDA	211284 (EDR Link)
Date of Submission	Jan 16, 2018
Generic Names	Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF)
Clinical Pharmacology Review Team	Vikram Arya, Ph.D., FCP, Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Celltrion, INC
Application Type	505 (b) (2)
Formulation; strength(s) to-be-marketed	Fixed Dose Combination (FDC) Tablets; 300 mg 3TC/300 mg TDF

Background

Celltrion INC (applicant) is seeking approval of Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF) 300 mg/300 mg FDC tablets based on the results of trial CT-G02 1.2, a single dose relative bioavailability trial conducted under *fasting conditions* and CT-G02 1.1, a single dose relative bioavailability trial conducted under *fed conditions*. The clinical pharmacology review of both relative bioavailability trials was checked into DARRTS on 09/13/2018.

The applicant did not provide adequate storage stability data to cover the entire duration of sample storage. For both trials, 44 days of storage stability data at ~-70 °C was provided whereas the samples were stored for 134 days (for samples collected in trial CT-G02 1.2) and for 129 days (for samples collected in trial CT-G02 1.1). The Office of Clinical Pharmacology (OCP) reviewed the information provided in the NDA and concluded that the information supports the approval of the application **pending acceptability of the additional storage stability data**. The applicant was requested (on 09/14/2018) to provide additional storage stability data to cover the entire duration of sample storage.

This addendum includes an assessment of the additional stability data provided by the applicant on 09/17/2018.

Additional Sample Storage Stability Data ([EDR Link](#))

Quality control samples at high and low concentrations of tenofovir and lamivudine were prepared on 29 September 2017 and stored frozen at ~ -70°C in human K₂EDTA plasma in polypropylene tubes until used. On 07 March 2018, the samples were thawed in a water bath at 22°C and assayed with a set of freshly prepared calibration standards and quality control samples.

The table below compares the concentrations of tenofovir and lamivudine in the stored samples with the freshly prepared QC samples at two different concentrations.

Table 1: Comparison of the tenofovir and lamivudine in the stored samples with the freshly prepared QC samples at two different concentrations

Replicates	Tenofovir		Lamivudine	
	High Concentration (450 ng/ml)	Low Concentration (14.0 ng/ml)	High Concentration (3750 ng/ml)	Low Concentration (117.0 ng/ml)
1	458	14.2	3669	117.5
2	467	14.4	3905	120.4
3	454	14.5	3644	121.9
4	470	14.8	3632	120.9
5	456	15.5	3742	122.1
6	471	13.8	3836	122.1
Mean	463	14.5	3738	120.8
% CV	1.6	4.0	3.0	1.5
% Bias	2.9	3.6	-0.3	3.2
N	6	6	6	6

Source: Method Validation Report-Addendum 1, Page 18

Conclusion

The applicant has demonstrated adequate long-term storage stability of tenofovir and lamivudine at ~-70°C in human K₂EDTA plasma for 159 days. The information provided by the applicant addresses the clinical pharmacology comment regarding lack of long term sample storage stability data in the original review and there are no remaining clinical pharmacology issues that would preclude approval of the application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIKRAM ARYA
10/21/2018

KELLIE S REYNOLDS
10/22/2018

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA	211284 (EDR Link)
Date of Submission	Jan 16, 2018
Generic Names	Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF)
Clinical Pharmacology Review Team	Vikram Arya, Ph.D., FCP, Islam Younis, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Celltrion, INC
Application Type	505 (b) (2)
Formulation; strength(s) to-be-marketed	Fixed Dose Combination (FDC) Tablets; 300 mg 3TC/300 mg TDF
Submission Type	NDA Submitted under the PEPFAR Program
Review Type	Standard Review

Overview

Celltrion INC (applicant) is seeking approval of Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF) 300 mg/300 mg FDC tablets for use under the President's Emergency Plan for AIDS Relief (PEPFAR) program. The individual reference products, Epivir[®] (lamivudine 300 mg tablets) of GlaxoSmithKline, USA and Viread[®] (Tenofovir Disoproxil Fumarate 300 mg tablets) of Gilead Sciences, Inc. were used as reference products in trial [CT-G02 1.2](#), a single dose relative bioavailability trial conducted under *fasting conditions* and [CT-G02 1.1](#), a single dose relative bioavailability trial conducted under *fed conditions*.

The results from both trials showed that geometric mean ratio and 90 % confidence intervals of C_{max} and $AUC_{0-\infty}$ for [3TC](#) and [TFV](#) (under fasting conditions) and [3TC](#) and [TFV](#) (under fed conditions) after administration of the test and reference product lie within the pre-specified 20 % boundary for demonstrating similarity in systemic exposures. Please refer to the individual reviews for additional information. The Office of Study Integrity and Surveillance (OSIS) recommended acceptance of data from the clinical and bioanalytical sites for both trials without an on-site inspection. Please refer to OSIS's review dated February 26, 2018 for details.

The applicant did not provide adequate storage stability data to cover the entire duration of sample storage. For both trials, 44 days of storage stability data at ~-70 °C was provided whereas the samples were stored for 134 days (for samples collected in trial CT-G02 1.2) and for 129 days (for samples collected in trial CT-G02 1.1). The applicant will be requested to provide additional storage stability data to cover the entire duration of sample storage and an addendum to this review will be submitted after the receipt and review of the additional storage stability data.

Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA and the information provided supports the approval of the application pending acceptability of the additional storage stability data.

Individual Trial Reviews

Trial #: CT-G02 1.2 ((b) (4) Study # (b) (4) 231461)

Title

A Single Center, Single-Dose, Open-Label, Laboratory-Blind, Randomized, Two-Treatment, Two-Period Crossover Study to Determine the Bioequivalence of a New Fixed Dose Combination Film-Coated Tablet Formulation containing 300 mg Tenofovir Disoproxil Fumarate and 300 mg Lamivudine against Viread® Film-Coated tablets containing 300 mg Tenofovir Disoproxil Fumarate and Epivir® Film-Coated Tablets containing 300 mg Lamivudine in healthy males and females under fasting conditions ([EDR Link](#))

Trial Period

(b) (4) (First subject first visit to last subject last visit)

Trial Design

Single dose, open label, randomized, two-treatment, two-period crossover study. Subjects randomized to treatment sequence 1 received test treatment in the first period and reference treatment in the second period under fasting conditions and subjects randomized to treatment sequence 2 received reference treatment in period 1 and test treatment in period 2 under fasting conditions. Each treatment was separated by a washout period of at least 7 days.

Test Treatment: Single tablet of 300 mg TDF/300 mg 3TC FDC

Reference treatment: One tablet each of EPIVIR® (300 mg) and VIREAD® (300 mg).

Identity of Investigational Products

The batch number and expiry date of the various treatments administered was as follows:

Viread® 300 mg tablets: Batch # 007657; Expiry Date: April 2021

Epivir® 300 mg tablets: Batch # 5ZP1465; Expiry Date: January 2018

TDF/3TC 300 mg/300 mg FDC tablets: Batch # CBAU002F; Expiry Date: December 10, 2017

Sample Collection and Pharmacokinetic Analysis

Blood samples were collected at pre-dose and up to 48 hours post dose to assess the plasma concentrations of 3TC and TFV using LC-MS/MS methods. The PK parameters were calculated by non-compartmental methods based on the actual sampling time intervals.

Results

Table 1 shows the bioanalytical assay parameters.

Table 1: Bioanalytical assay parameters

Link to Reports	TFV and 3TC		
Method Type	LC-MS/MS	Matrix	Human Plasma
Analytes	TFV and 3TC		
Calibration Range	TFV: 4.69 to 600 ng/mL 3TC: 39.06 to 5000 ng/mL		
Storage Conditions	TFV and 3TC shown to be stable in human K ₂ EDTA plasma for 44 days for at approximately -70°C. Applicant indicates that stability will be assessed over a longer time period and the results of the assessment will be provided in an addendum to the method validation report.		
QC Sample Concentrations	TFV: 14, 28, 56, 113, 225, 450 and 900 ng/mL (dilution QC) 3TC: 39.06, 117, 234, 469, 938, 1875, 3750 and 7500 ng/mL (dilution QC)		
Precision and Accuracy	TFV: Precision (% CV): 3.3 % to 7.7 %; % bias: -7.1 % to 1.1%. 3TC: Precision (% CV): 2.1 % to 15.5 %; % bias: -2.1 % to 1.5 %.		

Source: Bioanalytical report (links are provided in the table).

According to page 12 of the bioanalytical report, the maximum duration of storage of the samples (from the first collection date [(b) (4)] at the clinical site to the final date of analysis (November 23, 2017) at ~ -70 °C was 134 days (end date included). The applicant demonstrated long term stability for 44 days, hence the available storage stability data does not support the duration of the storage of the plasma samples. The applicant will be asked to provide additional stability data to support the duration of sample storage.

The other components of the bioanalytical method were found to be acceptable.

Subject Disposition and Demographics

Forty-eight (48) subjects were enrolled in the trial. One subject (subject # (b) (6)) withdrew from the trial during treatment period 2 for personal reasons; the remainder of the subjects completed both treatment phases. Subjects had mean (range) weight of 66.46 (50.8-100.2 kg), height 167.5 (148-185 cm), age 26.7 (18-40 years), and BMI 23.66 (19.8-29.3) kg/m².

Protocol Deviations

Protocol deviations were noted from the scheduled sample times for collection of the PK blood samples. Overall, the deviations are not expected to alter the conclusions of the trial because the sponsor used the actual sampling time (and not the scheduled sampling time) for PK analysis.

Concomitant Medications

No prior medication was recorded in the trial. During the trial, Subject (b) (6) ingested 1000 mg paracetamol daily for treatment of toothache. Other concomitant medications recorded were contraceptives which started before administration of the various treatments. The recorded concomitant medications were not considered to have interacted pharmacokinetically with test or reference products' pharmacokinetic profiles. To the Investigator's knowledge, all other subjects adhered to the restrictions.

Pharmacokinetic and Statistical Analysis

TFV:

Table 2 shows the arithmetic mean (\pm SD) of the various pharmacokinetic parameters of TFV for the test and reference product under fasting conditions.

Table 2: Arithmetic mean (\pm SD) of the various pharmacokinetic parameters of TFV for the test and reference product under fasting conditions

Statistic	C _{max} (ng/mL)	AUC _(0-t) (h*ng/mL)	AUC _(0-∞) (h*ng/mL)	T _{max} (h)	λ _z (/h)	t _{1/2} (h)
Test Product (T)						
n	47	47	47	47	47	47
Arithmetic Mean	289.8	1940	2191	1.081	0.04432	15.82
SD	79.90	522.4	603.6	0.411	0.004737	1.745
Reference Product (R)						
n	47	47	47	47	47	47
Arithmetic Mean	313.6	1971	2224	0.872	0.04431	15.89
SD	89.30	472.9	556.3	0.364	0.005543	2.068

Source: Clinical Trial Report, Page 56.

Table 3 shows the geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of TFV after administration of the test product and reference product under fasting conditions.

Table 3: Geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of TFV after administration of the test product and reference product under fasting conditions

Parameters (Unit)	Geometric LS Mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC _{0-inf} (h*ng/mL)	2110.65	2160.87	97.68	93.70	101.82
AUC _{0-t} (h*ng/mL)	1871.10	1919.95	97.46	93.64	101.42
C _{max} (ng/mL)	278.54	302.73	92.01	86.98	97.33

Source: Clinical Trial Report, Page 57.

3TC:

Table 4 shows the arithmetic mean (\pm SD) of the various pharmacokinetic parameters of 3TC for the test and reference product under fasting conditions.

Table 4: Arithmetic mean (\pm SD) of the various pharmacokinetic parameters of 3TC for the test and reference product under fasting conditions.

Statistic	C _{max} (ng/mL)	AUC _(0-t) (h*ng/mL)	AUC _(0-∞) (h*ng/mL)	T _{max} (h)	λ_z (/h)	t _{1/2} (h)
Test Product (T)						
n	47	47	47	47	47	47
Arithmetic Mean	2680	10950	11240	1.345	0.2061	3.750
SD	639.9	2569	2557	0.471	0.05808	1.528
Reference Product (R)						
n	47	47	47	47	47	47
Arithmetic Mean	2671	11050	11370	1.228	0.1978	4.069
SD	785.8	2612	2586	0.433	0.05222	2.957

Source: Clinical Study Report; page 57.

Table 5 shows the geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of 3TC after administration of the test product and reference product under fasting conditions.

Table 5: Geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of 3TC after administration of the test product and reference product under fasting conditions

Parameters	Geometric LS Mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC _{0-inf} (h*ng/mL)	10974.94	11095.51	98.91	94.48	103.55
AUC _{0-t} (h*ng/mL)	10670.93	10762.62	99.15	94.52	104.00
C _{max} (ng/mL)	2606.19	2570.20	101.40	96.05	107.05

Source: Clinical Study Report; page 58.

Conclusion

The results of the trial demonstrate similarity in the systemic exposures of TFV and 3TC after administration of the test and reference product under fasting conditions.

Trial #: CT-G02 1.1 ((b) (4) **Study #** (b) (4) **231460**)

Title

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Trial Period

(b) (4) (First subject first visit to last subject last visit)

Trial Design

Single dose, open label, randomized, two-treatment, two-period crossover study. After an overnight fast of at least 10 hours, subjects received a high fat, high calorie breakfast (989.8 kcal, 66.1 gms fat). Subjects randomized to treatment sequence 1 received test treatment in the first period and reference treatment in the second period under fed conditions and subjects randomized to treatment sequence 2 received reference treatment in period 1 and test treatment in period 2 under fed conditions. Each treatment was separated by a washout period of at least 7 days.

Test Treatment: Single tablet of 300 mg TDF/300 mg 3TC FDC

Reference treatment: One tablet each of EPIVIR® (300 mg) and VIREAD® (300 mg).

Identity of Investigational Products

The batch number and expiry date of the various treatments administered was as follows:

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Sample Collection and Pharmacokinetic Analysis

Blood samples were collected at pre-dose and up to 48 hours post dose to assess the plasma concentrations of 3TC and TFV using LC-MS/MS methods. The PK parameters were calculated by non-compartmental methods based on the actual sampling time intervals.

Results

Table 1 shows the bioanalytical assay parameters.

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QC Sample Concentrations	TFV: 14, 28, 56, 113, 225, 450 ng/mL 3TC: 117, 234, 469, 938, 1875, 3750 ng/mL		
Precision and Accuracy	TFV: Precision (% CV): 2.5 % to 4.6 %; % bias: -0.7 % to 0.9%. 3TC: Precision (% CV): 2.9 % to 5 %; % bias: -0.7 % to 1.6 %.		

Source: Bioanalytical report (links are provided in the table).

According to page 12 of the bioanalytical report, the maximum duration of storage of the samples (from the first collection date [(b) (4)] at the clinical site to the final date of analysis (November 29, 2017) at ~ -70 °C was 129 days (end date included). The applicant demonstrated demonstrated long term stability for 44 days, hence the available storage stability data does not support the duration of the storage of the plasma samples. The applicant will be asked to provide additional stability data to support the duration of sample storage.

The other components of the bioanalytical method were found to be acceptable.

Subject Disposition and Demographics

Forty-eight (48) subjects were enrolled in the trial. Three subjects were withdrawn from the study during treatment period 1 because of protocol violations; forty-five (45) subjects completed both treatment phases. Subjects had mean (range) weight of 67.66 (50.8-88.3 kg), height 167.4 (148-185 cm), age 25.6 (18-37 years), and BMI 24.16 (18.5-29.8) kg/m².

Protocol Deviations

- Deviations from the scheduled sampling times for collection of the PK blood samples were reported, however, the deviations are not expected to alter the conclusions of the trial because the sponsor used the actual sampling time (and not the scheduled sampling time) for PK analysis.
- Due to an oversight by the study staff, Subject (b) (6) started eating the high-fat, high-calorie breakfast 31 minutes (instead of 30 minutes) prior to administration of the investigational products in Treatment Period 1.
- At 12:00 on (b) (6) (Day 2 of Treatment Period 1) Subject (b) (6) consumed food containing citrus fruit (slice of lemon). This incident was reported on Day 2 when the 36-hour post-dose PK sample was collected at 19:34. The subject continued in the study at the discretion of the investigator.
- During the washout period, Subject (b) (6) ingested 15 mg of meloxicam, a NSAID, on (b) (6) as prescribed by the investigator. In total 30 mg meloxicam was ingested. The subject complaint about persistent pain in his left foot that was not relieved by using paracetamol tablets as prescribed by the investigator. Due to the discomfort and pain, the use of NSAIDs as concomitant medication for this subject was carefully considered by the investigator when prescribed.
- Due to an oversight by the study staff, the pre-dose vital signs for Subjects (b) (6) (b) (6) for Treatment Period 2 were performed outside of the -90 minutes specification according to the Window Allowance Document (WAD).

Overall, none of the deviations listed above are expected to alter the conclusions of the trial.

Pharmacokinetic and Statistical Analysis

Out of the 45 subjects who completed the study, one subject (subject # (b) (6)) was excluded from the PK analysis population as the last sample was collected 23.5 hours late and the PK parameter calculation was not conducted. Hence, the data from 44 subjects were included in the pharmacokinetic and statistical analysis.

TFV:

Table 2 shows the arithmetic mean (\pm SD) of the various pharmacokinetic parameters of TFV for the test and reference product under fed conditions.

Table 2: Arithmetic mean (\pm SD) of the various pharmacokinetic parameters of TFV for the test and reference product under fed conditions

Statistic	C_{max} (ng/mL)	$AUC_{(0-t)}$ (h \cdot ng/mL)	$AUC_{(0-\infty)}$ (h \cdot ng/mL)	T_{max} (h)	λ_z (/h)	$t_{1/2}$ (h)
Test Product (T)						
n	44	44	44	44	44	44
Arithmetic Mean	297.3	2413	2683	1.580	0.04724	14.77
SD	93.46	549.5	607.2	0.653	0.003906	1.244
Reference Product (R)						
n	44	44	44	44	44	44
Arithmetic Mean	284.4	2388	2665	1.320	0.04656	15.07
SD	91.32	585.6	652.6	0.484	0.005214	1.705

Source: Clinical Trial Report, Page 58.

Table 3 shows the geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of TFV after administration of the test product and reference product under fed conditions.

Table 3: Geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of TFV after administration of the test product and reference product under fed conditions

Parameters	Geometric LS Mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-inf}	2612.12	2585.89	101.01	97.67	104.47
AUC_{0-t}	2349.05	2316.27	101.42	98.00	104.94
C_{max}	282.39	270.38	104.44	99.09	110.08

Source: Clinical Trial Report, Page 59.

3TC:

Table 4 shows the arithmetic mean (\pm SD) of the various pharmacokinetic parameters of 3TC for the test and reference product under fed conditions.

Table 4: Arithmetic mean (\pm SD) of the various pharmacokinetic parameters of 3TC for the test and reference product under fed conditions

Statistic	C _{max} (ng/mL)	AUC _(0-t) (h*ng/mL)	AUC _(0-∞) (h*ng/mL)	T _{max} (h)	λ _z (/h)	t _{1/2} (h)
Test Product (T)						
n	44	44	44	44	44	44
Arithmetic Mean	2334	9375	9649	1.508	0.2119	3.465
SD	533.9	1599	1613	0.578	0.04566	0.9722
Reference Product (R)						
n	44	44	44	44	44	44
Arithmetic Mean	2253	9444	9779	1.477	0.1950	4.477
SD	567.4	1637	1654	0.675	0.06094	3.673

Source: Clinical Study Report; page 59.

Table 5 shows the geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of 3TC after administration of the test product and reference product under fed conditions.

Table 5: Geometric least squares mean, ratio of geometric least squares mean, intra subject variability, power and 90 % CI of various PK parameters of 3TC after administration of the test product and reference product under fed conditions

Parameters	Geometric LS Mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC _{0-inf}	9515.95	9639.33	98.72	95.99	101.53
AUC _{0-t}	9241.21	9301.60	99.35	96.54	102.24
C _{max}	2271.48	2183.36	104.04	97.87	110.59

Source: Clinical Study Report; page 60.

Conclusion

The results of the trial demonstrate similarity in the systemic exposures of TFV and 3TC after administration of the test and reference product under fed conditions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIKRAM ARYA
09/13/2018

ISLAM R YOUNIS
09/13/2018