OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA	210649
Date of Submission	September 14, 2017
Generic Names	Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate
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	Macleods Pharmaceuticals Limited, India
Application Type	505 (b) (2)
Formulation; strength(s) to-be-marketed	Fixed Dose Combination Tablets (FDC); 400 mg efavirenz/300 mg lamivudine/300 mg tenofovir DF
Submission Type	NDA Submitted Under PEPFAR Program
Review Classification	Priority

1 Regulatory Background

Macleods Pharmaceuticals Limited, India (applicant) is seeking approval of Fixed Dose Combination (FDC) tablets of Efavirenz (EFV), Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF) 400/300/300 mg. The individual reference products Efamat (efavirenz 200 mg) of Mylan Laboratories Ltd., India, Epivir® (lamivudine 300 mg tablets) of GlaxoSmithKline, USA and Viread® (Tenofovir Disoproxil Fumarate 300 mg tablets) of Gilead Sciences, Inc, USA were used as reference products.

The applicant obtained right of reference to ENCORE1, a randomized, double-blind, active-controlled, two-arm, parallel groups multinational clinical trial which demonstrated efficacy of EFV 400 mg dose relative to EFV 600 mg dose (in both treatment arms, EFV 400 mg or 600 mg was administered once daily in combination with Truvada®, a FDC of emtricitabine (FTC, 200 mg) and TDF (300 mg)). Please refer to the clinical review of ENCORE 1 for further details. The results from trial BEQ-1748-ELT(F)-2016 (which used Efamat as one of the reference product) bridges the efficacy and safety information from ENCORE1 to the EFV/3TC/TDF 400/300/300 mg FDC tablet because Efamat was the EFV formulation used in ENCORE1.

In this NDA (NDA #210649), the applicant provided the results from the following trial:

BEQ-1748-ELT(F)-2016: Assessment of the relative bioavailability of EFV/3TC/TFV 400/300/300 mg tablets (test treatment) relative to EFV 400 mg, 3TC 300 mg and TDF 300 mg (administered as individual products; reference treatment) after **single dose** administration under **fasting conditions.** Because the prescribing information of SUSTIVA® (efavirenz) recommends that SUSTIVA® be administered under fasting conditions, a relative bioavailability trial under fed conditions is not needed. The results of the trial show that the geometric mean ratio and 90 % confidence intervals of C_{max} and $AUC_{0-\infty}$ (AUC_{0-72} for EFV) for EFV, 3TC and TFV 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 clinical and bioanalytical assessments were conducted at the Bioanalytical Department of Macleods Pharmaceuticals. The Office of Study Integrity and Surveillance (OSIS) recommended acceptance of data from the clinical and bioanalytical sites without an on-site inspection. Please refer to OSIS's review dated November 21, 2017 for additional information.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA and the information provided supports the approval of the application.

2 Appendices

2.1 Individual Trial Review (BEQ-1748-ELT(F)-2016)

Title

Single dose fasting In Vivo Bioequivalence Study of fixed dose combination of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets 400 mg/300 mg/300 mg (Macleods Pharmaceuticals Ltd., India) in comparison with separate formulation of two tablets of Efavirenz tablets USP 200 mg (Mylan laboratories Ltd., India), one tablet of EPIVIR® (lamivudine) tablets 300 mg (Glaxo SmithKline, USA) and one tablet of VIREAD® (tenofovir disoproxil fumarate) Tablets 300 mg (Gilead Sciences, Inc., USA) in healthy, adult, human subjects.

Trial Period

Duration of Clinical Phase: February 7, 2017 through April 14, 2017
Duration of Bioanalytical Phase: March 20, 2017 through April 12, 2017
Date of Final Report: May 3, 2017

Trial Objectives

1) To evaluate the comparative oral bioavailability of single dose of fixed dose combination of Efavirenz/Lamivudine/Tenofovir disoproxil fumarate tablets 400 mg/300 mg/300 mg (Macleods Pharmaceuticals Ltd., India) [test treatment] in comparison with separate formulation of two tablets of Efavirenz tablets USP 200 mg (Mylan laboratories Ltd., India), one tablet of EPIVIR® (lamivudine) tablets 300 mg (Glaxo SmithKline, USA) and one tablet of VIREAD® (tenofovir disoproxil fumarate) Tablets 300 mg (Gilead Sciences, Inc., USA) [reference treatment] in healthy, adult, human subjects under fasting conditions.
2) To monitor the safety and tolerability of a single oral dose of efavirenz, lamivudine and tenofovir disoproxil fumarate Tablets 400 mg/ 300 mg/ 300 mg in healthy adult human subjects under fasting conditions.

Trial Design

Open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single dose, bioequivalence study in 36 healthy adult human subjects under fasting conditions.

There was a supervised overnight fasting period of at least 10 hours before dosing. Subjects were randomized to receive a single dose of either the test treatment or reference treatment as follows:

Test treatment: Single dose of FDC tablet of EFV/3TC/TDF (400/300/300 mg)
Reference treatment: Single dose of individually administered Efavirenz (b) (4) tablets (2X200 mg), EPIVIR® (1X300 mg) and VIREAD® (1X300 mg).

Reviewer's Note:

The applicant referred to Efavirenz (b) (4) tablets as one of the reference products in the trial. The applicant was asked (on 11/04/2017) to provide additional clarity regarding any potential differences between Efavirenz (b) (4) and Efamat. In response (received on 11/04/2017), the applicant confirmed that Efavirenz Tablets USP 200mg (Efamat) (Batch no. 3055579) provided by Mylan (manufacturer of Efamat) to Macleods USA are the same as used in the ENCORE 1 Study.

Identity of Investigational Products

Table 1 shows the identity of investigational products used in the trial.

Table 1: Identity of investigational products used in the trial

Treatment		Batch #	Manufacturing Date	Expiration Date	Manufactured By/For
Test Treatment	EFV/3TC/TDF 400/300/300 mg	BEB3601A	04/2016	03/2018	Macleods Pharmaceuticals Ltd.
Reference Treatment	Efavirenz (b) (4) tablets	3055579	July 2016	June 2018	Mylan Laboratories Ltd., India
	Epivir®	5ZP1465	Not Available	January 2018	ViiV Healthcare, North Carolina
	Viread®	005874	Not Available	June 2020	Gilead Sciences, CA

Source: Prepared by reviewer based on information provided on pages 48 and 49 of the final clinical study report.

Sample Collection and Pharmacokinetic Analysis

Blood samples were collected pre-dose and up to 72 hours post dose to assess the plasma concentrations of efavirenz, lamivudine, and tenofovir in plasma using LC-MS/MS methods. The statistical analysis was performed using SAS 9.4.

Results

Table 2 shows the bioanalytical assay parameters.

Table 2: Bioanalytical assay parameters

Link to Reports	EFV, 3TC and TFV		
Method Type	LC-MS/MS	Matrix	Human Plasma
Analytes	EFV, 3TC, TFV		
Calibration Range	EFV: 50.09 to 5054.19 ng/mL 3TC: 49.75 to 5020.03 ng/mL TFV: 50.01 to 600.10 ng/mL		
QC Sample Concentrations	EFV: 141.05, 810.27, 2010.68, and 4036.36 ng/mL 3TC: 140.06, 804.60, 1996.61, 4008.12 ng/mL TFV: 13.52, 100.01, 290.18, 500.06 ng/mL		
Storage Duration (first sample collection until completion of study sample analysis)	53 days at -75°C (for EFV and 3TC) 64 days at -75°C (for TFV)		
Long term stability in plasma	124 days at -75°C (for EFV and 3TC) 163 days below -50°C (for TFV)		
Precision and Accuracy	EFV: inter-day precision (% CV): 2.26% to 2.87%; inter-day accuracy (% nominal): 99.07% to 101.97 %. 3TC: inter-day precision (% CV): 4.07 % to 4.83%; inter-day accuracy (% nominal): 99.55 % to 101.59 %. TFV: inter-day precision (% CV): 1.93% to 3.70%; inter-day accuracy (% nominal): 95.31% to 99.23 %.		

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

The bioanalytical methods were found to be acceptable.

Subject Disposition and Demographics

A total of 36 subjects were planned and enrolled in the trial. Out of the 36 subjects, 33 subjects completed both periods of the trial. One subject (subject # (b) (6)) was withdrawn from the study in period 1 (post dose) due to an adverse event as determined by the principal investigator and two subjects (subject # (b) (6)) did not report to the facility for period 2 due to personal reasons, and thus were considered as dropped out from the study. Overall, data from 33 subjects was used for pharmacokinetics and statistical analysis.

The demographic data (mean ± sd) of the 33 subjects who completed the study were as follows: Age: 29 ± 6.2 (range 19-41 years), weight: 67.5 ± 6.43 (range 53-81.2 kg), and BMI: 23.9 ± 2.7 (range 19.26-29.47 kg/m^2)

Pharmacokinetic Analysis

The applicant noted deviations (difference between scheduled sample collection time and actual sample collection time) in PK sample collection (page 59-60 of the study report).

Per the protocol, blood samples were planned to be collected within 2 minutes of scheduled time for in-house samples and within one hour for ambulatory visit samples. The applicant noted six sample collection time point deviations in period 1 (maximum deviation was 0.07 hour) and five sample collection time point deviations in period 2 (maximum deviation was 1.13 hour). These deviations do not impact the conclusions of the trial because actual sampling time points were used in the pharmacokinetic analysis (as indicated in Section 9.7.1, Statistical and Analytical Plan, on Page 56 of the final study report).

For two subjects, 72-hour sample was missing (for subject (b) (6), the sample was missing in Period 1 and for subject (b) (6) the sample was missing in Period 2). These missing samples are not expected to alter the overall conclusions of the trial.

Table 3: Arithmetic mean (± SD), CV %, median and range of the various pharmacokinetic parameters of EFV for the test and reference product

Pharmacokinetic Parameters	Efavirenz - Test Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	1924.250	527.6796	27.42	1867.31	1009.44 - 2893.22
AUC_{0-72} (ng*hrs/mL)	36974.96871	9103.882344	24.62	36153.3733	24006.0011 - 58485.3462
T_{max} (hrs)	3.132	1.4663	46.82	3.50	1.00 - 6.00

Pharmacokinetic Parameters	Efavirenz - Reference Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	1741.395	515.4606	29.60	1651.46	868.25 - 2827.10
AUC_{0-72} (ng*hrs/mL)	36375.17545	8817.212464	24.24	37618.8336	22571.5677 - 57935.9647
T_{max} (hrs)	3.279	1.4180	43.24	4.00	0.83 - 5.00

Source: Clinical Study Report; page 61 of 80.

Table 4: Arithmetic mean (± SD), CV %, median and range of the various pharmacokinetic parameters of 3TC for the test and reference product

Pharmacokinetic Parameters	Lamivudine - Test Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	2505.368	654.5421	26.13	2508.90	990.18 - 3924.13
AUC_{0-t} (ng*hrs/mL)	12062.67895	2719.790528	22.55	11895.8029	6182.3897 - 16917.0273
$AUC_{0-\infty}$ (ng*hrs/mL)	12433.56890	2694.735966	21.67	12257.3862	6610.1139 - 17410.8011
T_{max} (hrs)	1.691	0.8720	51.56	1.33	0.83 - 5.00
$T_{1/2}$ (hrs)	3.93857	1.387680	35.23	3.6558	2.3125 - 7.6670
K_e (hrs^{-1})	0.19300	0.053315	27.62	0.1896	0.0904 - 0.2997

Pharmacokinetic Parameters	Lamivudine - Reference Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	2627.423	619.8833	23.59	2683.48	1232.19 - 3641.01
AUC_{0-t} (ng*hrs/mL)	11834.05900	2617.405556	22.12	11332.9671	7878.0015 - 17540.8330
$AUC_{0-\infty}$ (ng*hrs/mL)	12189.49780	2617.027955	21.47	11658.8171	8170.5931 - 17812.8201
T_{max} (hrs)	1.574	1.0461	66.47	1.17	0.67 - 5.50
$T_{1/2}$ (hrs)	4.00851	1.367118	34.11	3.6166	2.5731 - 7.5380
K_e (hrs^{-1})	0.18862	0.050274	26.65	0.1917	0.0920 - 0.2694

Source: Clinical Study Report; page 61 of 80.

Table 5: Arithmetic mean (± SD), CV %, median and range of the various pharmacokinetic parameters of TFV for the test and reference product

Pharmacokinetic Parameters	Tenofovir - Test Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	267.363	69.5581	26.02	276.29	146.93 - 443.95
AUC_{0-t} (ng*hrs/mL)	2152.89454	610.159235	28.34	2303.4648	1092.7276 - 3106.8472
$AUC_{0-\infty}$ (ng*hrs/mL)	2370.19681	629.116082	26.54	2492.8542	1169.2780 - 3409.2131
T_{max} (hrs)	1.429	0.7826	54.76	1.33	0.67 - 4.50
$T_{1/2}$ (hrs)	18.81541	3.296353	17.52	18.9107	9.6650 - 25.9660
K_e (hrs^{-1})	0.03823	0.008633	22.58	0.0367	0.0267 - 0.0717

Pharmacokinetic Parameters	Tenofovir - Reference Product (N=33)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	285.858	78.4703	27.45	270.50	175.04 - 413.12
AUC_{0-t} (ng*hrs/mL)	2151.39348	552.020461	25.66	2222.0585	1010.4510 - 3219.2228
$AUC_{0-\infty}$ (ng*hrs/mL)	2382.12200	527.275729	22.13	2503.9841	1180.5851 - 3377.7134
T_{max} (hrs)	1.142	0.5454	47.77	1.00	0.50 - 3.00
$T_{1/2}$ (hrs)	19.83775	3.205078	16.16	19.8198	14.3645 - 28.2652
K_e (hrs^{-1})	0.03583	0.005775	16.12	0.0350	0.0245 - 0.0483

Source: Clinical Study Report; page 62 of 80.

Statistical Analysis

Table 6: Geometric least squares mean, ratio of geometric least squares means, intra subject variability, power and 90 % CI of EFV after administration of the test product and reference product

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90% Confidence Interval for Efavirenz (N= 33 Subjects)						
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90\% Confidence Interval (%)
	Test(T)	Reference (R)				
C_{max} (ng/mL)	1848.391	1666.149	110.94	18.97	99.54	102.56 - 120.00
AUC_{0-72} (ng*hrs/mL)	35847.472	35247.939	101.70	12.63	100.00	96.50 - 107.19

Source: Clinical Study Report; page 62 of 80.

Table 7: Geometric least squares mean, ratio of geometric least squares means, intra subject variability, power and 90 % CI of 3TC after administration of the test product and reference product

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90% Confidence Interval for Lamivudine (N= 33 Subjects)						
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	2409.698	2540.373	94.86	16.42	99.93	88.61 - 101.54
AUC_{0-t} (ng*hrs/mL)	11737.812	11532.593	101.78	18.45	99.67	94.29 - 109.86
$AUC_{0-\infty}$ (ng*hrs/mL)	12128.787	11896.456	101.95	17.47	99.84	94.83 - 109.61

Source: Clinical Study Report; page 62 of 80.

Table 8: Geometric least squares mean, ratio of geometric least squares means, intra subject variability, power and 90 % CI of TFV after administration of the test product and reference product

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90% Confidence Interval for Tenofovir (N= 33 Subjects)						
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90% Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	258.248	275.321	93.80	15.09	99.98	88.10 - 99.86
AUC_{0-t} (ng*hrs/mL)	2058.917	2073.420	99.30	16.55	99.92	92.71 - 106.36
$AUC_{0-\infty}$ (ng*hrs/mL)	2279.087	2317.171	98.36	15.05	99.98	92.40 - 104.70

Source: Clinical Study Report; page 63 of 80.

Conclusion

The results of the trial demonstrate similarity in the systemic exposures of EFV, 3TC and TFV after administration of the test and reference product under fasting 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
03/05/2019 12:37:04 PM

KELLIE S REYNOLDS
03/05/2019 12:51:08 PM