Clinical trial results:
A Study of the Comparative Bioavailability of Two Investigational Pediatric Oral Granule Formulations of Lamivudine and Tenofovir Compared to the Adult Marketed Formulations

Summary

EudraCT number	2016-004392-41
Trial protocol	Outside EU/EEA
Global end of trial date	25 January 2017

Results information

Result version number	v1 (current)
This version publication date	21 December 2017
First version publication date	21 December 2017

Trial information

Trial identification

Sponsor protocol code	1439a-054

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-1439A-054

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, Kenilworth, NJ,
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001695-PIP01-14
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2016
Global end of trial reached?	Yes
Global end of trial date	25 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to compare the bioavailability of pediatric formulations with the adult marketed formulations of lamivudine and tenofovir disoproxil fumarate (TDF) administered as single, oral doses to adult healthy males and females.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Healthy, non-smoking, males and females, from 18 to 55 years of age were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Enrolled Participants

Arm description:

The 14 treatments were as follows: 1) one lamivudine tablet followed by one tenofovir (TDF) tablet; 2) 60 lamivudine uncoated granules (UG) followed by 60 TDF UG; 3) 60 lamivudine coated OG (CG) followed by 60 TDF CG; 4) one TDF tablet followed by one lamivudine tablet; 5) 60 TDF UG followed by 60 lamivudine UG; 6) 60 TDF CG followed by 60 lamivudine CG; 7) 60 lamivudine UG in vanilla pudding (VP) followed by 60 TDF UG in VP; 8) 60 lamivudine UG in applesauce (AS) followed by 60 TDF UG in AS; 9) 60 lamivudine CG in VP followed by 60 TDF CG in VP; 10) 60 lamivudine CG in AS followed by 60 TDF CG in AS; 11) 60 TDF UG in VP followed by 60 lamivudine UG in VP; 12) 60 TDF pediatric UG in AS followed by 60 lamivudine UG in AS; 13) 60 TDF CG in VP followed by 60 lamivudine CG in VP; 14) 60 TDF CG in AS followed by 60 lamivudine CG in AS.

Arm type	Experimental
Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 300 mg of lamivudine adult oral tablets or 60 pediatric x 5-mg uncoated or coated oral granules (administered alone, with vanilla pudding, or with applesauce).

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	TDF
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 300 mg of lamivudine adult oral tablets or 60 pediatric x 5-mg uncoated or coated oral granules (administered alone, with vanilla pudding, or with applesauce).

Number of subjects in period 1	All Enrolled Participants
Started	24
Completed	22
Not completed	2
Adverse event, non-fatal	1

Non-compliance with protocol restrictions	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All Enrolled Participants	

Reporting group values	Overall Study	Total	
Number of subjects	24	24	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	39.0		
standard deviation	± 8.6	-	
Gender Categorical Units: Subjects			
Female	19	19	
Male	5	5	

End points

End points reporting groups

Reporting group title	All Enrolled Participants
Reporting group description:	
The 14 treatments were as follows: 1) one lamivudine tablet followed by one tenofovir (TDF) tablet; 2) 60 lamivudine uncoated granules (UG) followed by 60 TDF UG; 3) 60 lamivudine coated OG (CG) followed by 60 TDF CG; 4) one TDF tablet followed by one lamivudine tablet; 5) 60 TDF UG followed by 60 lamivudine UG; 6) 60 TDF CG followed by 60 lamivudine CG; 7) 60 lamivudine UG in vanilla pudding (VP) followed by 60 TDF UG in VP; 8) 60 lamivudine UG in applesauce (AS) followed by 60 TDF UG in AS; 9) 60 lamivudine CG in VP followed by 60 TDF CG in VP; 10) 60 lamivudine CG in AS followed by 60 TDF CG in AS; 11) 60 TDF UG in VP followed by 60 lamivudine UG in VP; 12) 60 TDF pediatric UG in AS followed by 60 lamivudine UG in AS; 13) 60 TDF CG in VP followed by 60 lamivudine CG in VP; 14) 60 TDF CG in AS followed by 60 lamivudine CG in AS.	
Subject analysis set title	300 mg lamivudine adult tablet + tenofovir
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine adult tablet followed by a single oral dose of 300 mg tenofovir adult tablet	
Subject analysis set title	300 mg lamivudine uncoated granules + tenofovir
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules followed by a single oral dose of 300 mg tenofovir pediatric uncoated granules	
Subject analysis set title	300 mg lamivudine coated granules + tenofovir
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules followed by a single oral dose of 300 mg tenofovir pediatric coated oral granules	
Subject analysis set title	300 mg tenofovir adult tablet + lamivudine
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir adult tablet followed by a single oral dose of 300 mg lamivudine adult tablet	
Subject analysis set title	300 mg tenofovir uncoated granules + lamivudine
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric uncoated granules followed by a single oral dose of 300 mg lamivudine pediatric uncoated granules	
Subject analysis set title	300 mg tenofovir coated granules + lamivudine
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric coated granules followed by a single oral dose of 300 mg lamivudine pediatric coated granules	
Subject analysis set title	300 mg lamivudine uncoated granules + tenofovir in pudding
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules followed by a single oral dose of 300 mg tenofovir pediatric uncoated granules in pudding	
Subject analysis set title	300 mg lamivudine uncoated granules + tenofovir in applesauce
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules followed by a single oral dose of 300 mg tenofovir pediatric uncoated granules in applesauce	
Subject analysis set title	300 mg tenofovir uncoated granules + lamivudine in pudding

Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric uncoated granules followed by a single oral dose of 300 mg lamivudine pediatric uncoated granules in pudding	
Subject analysis set title	300 mg tenofovir uncoated granules + lamivudine in applesauce
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric uncoated granules followed by a single oral dose of 300 mg lamivudine pediatric uncoated granules in applesauce	
Subject analysis set title	300 mg lamivudine coated granules + tenofovir in pudding
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules followed by a single oral dose of 300 mg tenofovir pediatric coated granules in pudding	
Subject analysis set title	300 mg lamivudine coated granules + tenofovir in applesauce
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules followed by a single oral dose of 300 mg tenofovir pediatric coated granules in applesauce	
Subject analysis set title	300 mg tenofovir coated granules + lamivudine in pudding
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric coated granules followed by a single oral dose of 300 mg lamivudine pediatric coated granules in pudding	
Subject analysis set title	300 mg tenofovir coated granules + lamivudine in applesauce
Subject analysis set type	Per protocol
Subject analysis set description:	
Under fasted conditions a single oral dose of 300 mg tenofovir pediatric coated granules followed by a single oral dose of 300 mg lamivudine pediatric coated granules in applesauce	

Primary: Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of plasma lamivudine

End point title	Area under the concentration-time curve from time 0 to infinity (AUC0-inf) of plasma lamivudine
End point description:	
Participants were treated with a single oral dose of 300 mg lamivudine with 300 mg of tenofovir. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the AUC0-inf of plasma lamivudine. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.	
End point type	Primary
End point timeframe:	
Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose	

End point values	300 mg lamivudine adult tablet + tenofovir	300 mg lamivudine uncoated granules + tenofovir	300 mg lamivudine coated granules + tenofovir	300 mg lamivudine uncoated granules + tenofovir in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: hr*ng/mL				
geometric mean (confidence interval	14100 (13200	14100 (13400	14100 (13400	11000 (10200

95%)	to 15100)	to 14800)	to 14800)	to 12000)

End point values	300 mg lamivudine uncoated granules + tenofovir in applesauce	300 mg lamivudine coated granules + tenofovir in pudding	300 mg lamivudine coated granules + tenofovir in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	9	10	
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	11100 (10200 to 12100)	11900 (10500 to 13400)	12200 (11400 to 13000)	

Statistical analyses

Statistical analysis title	Lamivudine: Uncoated Granules / Adult Tablet
Statistical analysis description:	
Geometric mean ratio (GMR) of 300 mg lamivudine uncoated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir	
Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine adult tablet + tenofovir
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	GMR
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.03

Notes:

[1] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine: Coated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg lamivudine coated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir	
Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine coated granules + tenofovir
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	GMR
Point estimate	1

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.03

Notes:

[2] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Uncoated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	GMR
Point estimate	0.78
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	0.83

Notes:

[3] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Uncoated Granules:Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	GMR
Point estimate	0.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.75
upper limit	0.83

Notes:

[4] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in pudding

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	GMR
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	0.92

Notes:

[5] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in applesauce
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	GMR
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	0.91

Notes:

[6] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: AUC0-inf of plasma tenofovir

End point title	AUC0-inf of plasma tenofovir

End point description:

Participants were treated with a single oral dose of 300 mg tenofovir with 300 mg of lamivudine. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the AUC0-inf of plasma tenofovir. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose

End point values	300 mg tenofovir adult tablet + lamivudine	300 mg tenofovir uncoated granules + lamivudine	300 mg tenofovir coated granules + lamivudine	300 mg tenofovir uncoated granules + lamivudine in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	2800 (2450 to 3210)	2910 (2700 to 3150)	2920 (2680 to 3180)	3300 (2900 to 3760)

End point values	300 mg tenofovir uncoated granules + lamivudine in applesauce	300 mg tenofovir coated granules + lamivudine in pudding	300 mg tenofovir coated granules + lamivudine in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	3490 (2960 to 4130)	3450 (3180 to 3730)	3360 (3050 to 3710)	

Statistical analyses

Statistical analysis title	Tenofovir: Uncoated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg tenofovir uncoated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine	
Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir uncoated granules + lamivudine
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.12

Notes:

[7] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir: Coated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg tenofovir coated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine	
Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir coated granules + lamivudine

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.13

Notes:

[8] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Uncoated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	GMR
Point estimate	1.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.04
upper limit	1.23

Notes:

[9] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Uncoated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	GMR
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.07
upper limit	1.34

Notes:

[10] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	GMR
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.11
upper limit	1.25

Notes:

[11] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	GMR
Point estimate	1.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	1.23

Notes:

[12] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: Area under the concentration-time curve from time 0 to the last time point (AUC0-last) of plasma lamivudine

End point title	Area under the concentration-time curve from time 0 to the last time point (AUC0-last) of plasma lamivudine

End point description:

Participants were treated with a single oral dose of 300 mg lamivudine with 300 mg of tenofovir. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the AUC0-last of plasma lamivudine. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose

End point values	300 mg lamivudine adult tablet + tenofovir	300 mg lamivudine uncoated granules + tenofovir	300 mg lamivudine coated granules + tenofovir	300 mg lamivudine uncoated granules + tenofovir in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	14000 (13100 to 14900)	13900 (13200 to 14600)	13900 (13100 to 14600)	10900 (9960 to 11800)

End point values	300 mg lamivudine uncoated granules + tenofovir in applesauce	300 mg lamivudine coated granules + tenofovir in pudding	300 mg lamivudine coated granules + tenofovir in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	10900 (10000 to 11900)	11700 (10300 to 13200)	11700 (10900 to 12500)	

Statistical analyses

Statistical analysis title	Lamivudine: Uncoated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg lamivudine uncoated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir

Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine uncoated granules + tenofovir
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	GMR
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.04

Notes:

[13] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine: Coated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg lamivudine coated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir

Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine coated granules + tenofovir
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	GMR
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.03

Notes:

[14] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Uncoated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	GMR
Point estimate	0.78
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	0.83

Notes:

[15] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Uncoated Granules:Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	GMR
Point estimate	0.78

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	0.83

Notes:

[16] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[17]
Parameter estimate	GMR
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	0.91

Notes:

[17] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[18]
Parameter estimate	GMR
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	0.88

Notes:

[18] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: AUC0-last of plasma tenofovir

End point title	AUC0-last of plasma tenofovir

End point description:

Participants were treated with a single oral dose of 300 mg tenofovir with 300 mg of lamivudine. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the AUC0-last of plasma tenofovir. Plasma concentrations were natural log transformed, and a linear mixed effects

model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose

End point values	300 mg tenofovir adult tablet + lamivudine	300 mg tenofovir uncoated granules + lamivudine	300 mg tenofovir coated granules + lamivudine	300 mg tenofovir uncoated granules + lamivudine in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	2640 (2310 to 3020)	2740 (2540 to 2960)	2740 (2530 to 2980)	3100 (2730 to 3500)

End point values	300 mg tenofovir uncoated granules + lamivudine in applesauce	300 mg tenofovir coated granules + lamivudine in pudding	300 mg tenofovir coated granules + lamivudine in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: hr*ng/mL				
geometric mean (confidence interval 95%)	3250 (2750 to 3850)	3240 (3000 to 3500)	3140 (2860 to 3440)	

Statistical analyses

Statistical analysis title	Tenofovir: Uncoated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg tenofovir uncoated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine

Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir uncoated granules + lamivudine
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[19]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.13

Notes:

[19] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir: Coated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg tenofovir coated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine	
Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir coated granules + lamivudine
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[20]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.12

Notes:

[20] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Uncoated Granules: In Pudding / Alone
Statistical analysis description:	
GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone	
Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[21]
Parameter estimate	GMR
Point estimate	1.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.04
upper limit	1.22

Notes:

[21] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Uncoated Granules: In Applesauce / Alone
Statistical analysis description:	
GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone	
Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in applesauce

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	GMR
Point estimate	1.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	1.33

Notes:

[22] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[23]
Parameter estimate	GMR
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.11
upper limit	1.25

Notes:

[23] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[24]
Parameter estimate	GMR
Point estimate	1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.07
upper limit	1.22

Notes:

[24] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: Maximum concentration (Cmax) of plasma lamivudine

End point title	Maximum concentration (Cmax) of plasma lamivudine

End point description:

Participants were treated with a single oral dose of 300 mg lamivudine with 300 mg of tenofovir. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the Cmax of plasma lamivudine. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose

End point values	300 mg lamivudine adult tablet + tenofovir	300 mg lamivudine uncoated granules + tenofovir	300 mg lamivudine coated granules + tenofovir	300 mg lamivudine uncoated granules + tenofovir in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: ng/mL				
geometric mean (confidence interval 95%)	2990 (2600 to 3430)	3120 (2810 to 3460)	2970 (2610 to 3380)	2330 (2100 to 2590)

End point values	300 mg lamivudine uncoated granules + tenofovir in applesauce	300 mg lamivudine coated granules + tenofovir in pudding	300 mg lamivudine coated granules + tenofovir in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: ng/mL				
geometric mean (confidence interval 95%)	2540 (2240 to 2870)	2510 (2120 to 2960)	2500 (2060 to 3030)	

Statistical analyses

Statistical analysis title	Lamivudine: Uncoated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg lamivudine uncoated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir

Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine uncoated granules + tenofovir

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[25]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.13

Notes:

[25] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine: Coated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg lamivudine coated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir

Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine coated granules + tenofovir
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[26]
Parameter estimate	GMR
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.08

Notes:

[26] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Uncoated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[27]
Parameter estimate	GMR
Point estimate	0.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	0.81

Notes:

[27] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Uncoated Granules:Applesauce / Alone
Statistical analysis description:	
GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone	
Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[28]
Parameter estimate	GMR
Point estimate	0.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.75
upper limit	0.89

Notes:

[28] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Coated Granules: In Pudding / Alone
Statistical analysis description:	
GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone	
Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[29]
Parameter estimate	GMR
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.75
upper limit	0.95

Notes:

[29] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Coated Granules: In Applesauce / Alone
Statistical analysis description:	
GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone	
Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	GMR
Point estimate	0.84

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	0.96

Notes:

[30] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: Cmax of plasma tenofovir

End point title	Cmax of plasma tenofovir

End point description:

Participants were treated with a single oral dose of 300 mg tenofovir with 300 mg of lamivudine. Blood samples collected from pre-dose (0-hr) up to 72 hours post-dose were used to determine the Cmax of plasma tenofovir. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

Pre-dose (0-hr), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 48, and 72 hours post-dose

End point values	300 mg tenofovir adult tablet + lamivudine	300 mg tenofovir uncoated granules + lamivudine	300 mg tenofovir coated granules + lamivudine	300 mg tenofovir uncoated granules + lamivudine in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: ng/mL				
geometric mean (confidence interval 95%)	311 (270 to 358)	322 (292 to 355)	321 (288 to 357)	392 (343 to 448)

End point values	300 mg tenofovir uncoated granules + lamivudine in applesauce	300 mg tenofovir coated granules + lamivudine in pudding	300 mg tenofovir coated granules + lamivudine in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: ng/mL				
geometric mean (confidence interval 95%)	395 (321 to 486)	394 (352 to 441)	384 (336 to 439)	

Statistical analyses

Statistical analysis title	Tenofovir: Uncoated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg tenofovir uncoated granules with lamivudine / 300 mg tenofovir adult tablet with

lamivudine

Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir uncoated granules + lamivudine
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.14

Notes:

[31] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir: Coated Granules / Adult Tablet

Statistical analysis description:

GMR of 300 mg tenofovir coated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine

Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir coated granules + lamivudine
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[32]
Parameter estimate	GMR
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.14

Notes:

[32] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Uncoated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in pudding
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[33]
Parameter estimate	GMR
Point estimate	1.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1
upper limit	1.35

Notes:

[33] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Uncoated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[34]
Parameter estimate	GMR
Point estimate	1.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	1.43

Notes:

[34] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[35]
Parameter estimate	GMR
Point estimate	1.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.12
upper limit	1.35

Notes:

[35] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in applesauce

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[36]
Parameter estimate	GMR
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	1.33

Notes:

[36] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: Concentration at 24 hours post-dose (C24) of plasma lamivudine

End point title	Concentration at 24 hours post-dose (C24) of plasma lamivudine

End point description:

Participants were treated with a single oral dose of 300 mg lamivudine with 300 mg of tenofovir. Blood samples collected at 24 hours post-dose were used to determine the C24 of plasma lamivudine. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

24 hours post-dose

End point values	300 mg lamivudine adult tablet + tenofovir	300 mg lamivudine uncoated granules + tenofovir	300 mg lamivudine coated granules + tenofovir	300 mg lamivudine uncoated granules + tenofovir in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: ng/mL				
geometric mean (confidence interval 95%)	31.9 (28.9 to 35.2)	30.7 (28.1 to 33.6)	32.1 (29.1 to 35.5)	36.9 (32.0 to 42.5)

End point values	300 mg lamivudine uncoated granules + tenofovir in applesauce	300 mg lamivudine coated granules + tenofovir in pudding	300 mg lamivudine coated granules + tenofovir in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	
Units: ng/mL				
geometric mean (confidence interval 95%)	34.2 (27.0 to 43.4)	33.3 (29.9 to 37.0)	33.2 (30.0 to 36.7)	

Statistical analyses

Statistical analysis title	Lamivudine: Uncoated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg lamivudine uncoated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir	
Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine uncoated granules + tenofovir
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[37]
Parameter estimate	GMR
Point estimate	0.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.91
upper limit	1.02

Notes:

[37] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine: Coated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg lamivudine coated granules with tenofovir / 300 mg lamivudine adult tablet with tenofovir	
Comparison groups	300 mg lamivudine adult tablet + tenofovir v 300 mg lamivudine coated granules + tenofovir
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[38]
Parameter estimate	GMR
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.07

Notes:

[38] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Uncoated Granules: In Pudding / Alone
Statistical analysis description:	
GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone	
Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in pudding

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[39]
Parameter estimate	GMR
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.09
upper limit	1.32

Notes:

[39] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Uncoated Granules:Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine uncoated granules + tenofovir v 300 mg lamivudine uncoated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	GMR
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.31

Notes:

[40] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Lamivudine Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in pudding / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[41]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.12

Notes:

[41] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Lamivudine Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg lamivudine with tenofovir dosed in applesauce / 300 mg lamivudine with tenofovir dosed alone

Comparison groups	300 mg lamivudine coated granules + tenofovir v 300 mg lamivudine coated granules + tenofovir in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	GMR
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.11

Notes:

[42] - The same participants took both treatments; so the number analyzed is actually 24.

Primary: C24 of plasma tenofovir

End point title	C24 of plasma tenofovir

End point description:

Participants were treated with a single oral dose of 300 mg tenofovir with 300 mg of lamivudine. Blood samples collected at 24 hours post-dose were used to determine the C24 of plasma tenofovir. Plasma concentrations were natural log transformed, and a linear mixed effects model was used to generate back-transformed least square means and confidence intervals.

End point type	Primary

End point timeframe:

24 hours post-dose

End point values	300 mg tenofovir adult tablet + lamivudine	300 mg tenofovir uncoated granules + lamivudine	300 mg tenofovir coated granules + lamivudine	300 mg tenofovir uncoated granules + lamivudine in pudding
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	12
Units: ng/mL				
geometric mean (confidence interval 95%)	32.8 (28.4 to 37.9)	34.2 (31.7 to 37.0)	34.1 (31.6 to 36.7)	38.1 (33.7 to 42.9)

End point values	300 mg tenofovir uncoated granules + lamivudine in applesauce	300 mg tenofovir coated granules + lamivudine in pudding	300 mg tenofovir coated granules + lamivudine in applesauce	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	10	11	

Units: ng/mL				
geometric mean (confidence interval 95%)	40.5 (34.9 to 46.9)	40.9 (37.7 to 44.5)	38.5 (35.2 to 42.2)	

Statistical analyses

Statistical analysis title	Tenofovir: Uncoated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg tenofovir uncoated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine	
Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir uncoated granules + lamivudine
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.15

Notes:

[43] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir: Coated Granules / Adult Tablet
Statistical analysis description:	
GMR of 300 mg tenofovir coated granules with lamivudine / 300 mg tenofovir adult tablet with lamivudine	
Comparison groups	300 mg tenofovir adult tablet + lamivudine v 300 mg tenofovir coated granules + lamivudine
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[44]
Parameter estimate	GMR
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.14

Notes:

[44] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Uncoated Granules: In Pudding / Alone
Statistical analysis description:	
GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone	
Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in pudding

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[45]
Parameter estimate	GMR
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.02
upper limit	1.21

Notes:

[45] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Uncoated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir uncoated granules + lamivudine v 300 mg tenofovir uncoated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[46]
Parameter estimate	GMR
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.07
upper limit	1.31

Notes:

[46] - The same participants took both treatments; so the number analyzed is actually 23.

Statistical analysis title	Tenofovir Coated Granules: In Pudding / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in pudding / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in pudding
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[47]
Parameter estimate	GMR
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.13
upper limit	1.28

Notes:

[47] - The same participants took both treatments; so the number analyzed is actually 24.

Statistical analysis title	Tenofovir Coated Granules: In Applesauce / Alone

Statistical analysis description:

GMR of 300 mg tenofovir with lamivudine dosed in applesauce / 300 mg tenofovir with lamivudine dosed alone

Comparison groups	300 mg tenofovir coated granules + lamivudine v 300 mg tenofovir coated granules + lamivudine in applesauce
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[48]
Parameter estimate	GMR
Point estimate	1.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.06
upper limit	1.21

Notes:

[48] - The same participants took both treatments; so the number analyzed is actually 24.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7 days after each study treatment, and up to 14 days after the last treatment.

Adverse event reporting additional description:

All participants who received at least one dose of investigational drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Lamivudine 300 mg tablet + Tenofovir 300 mg tablet

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine adult tablet with a single oral dose of 300 mg tenofovir adult tablet

Reporting group title	Lamivudine 300 mg uncoated granules (UG) + Tenofovir 300 mg UG

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules with a single oral dose of 300 mg tenofovir pediatric uncoated granules

Reporting group title	Lamivudine 300 mg coated granules (CG) + Tenofovir 300 mg CG

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules with a single oral dose of 300 mg tenofovir pediatric coated granules

Reporting group title	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with pudding

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules with a single oral dose of 300 mg tenofovir pediatric uncoated granules, with pudding

Reporting group title	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with applesauce

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric uncoated granules with a single oral dose of 300 mg tenofovir pediatric uncoated granules, with applesauce

Reporting group title	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with pudding

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules with a single oral dose of 300 mg tenofovir pediatric coated granules, with pudding

Reporting group title	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with applesauce

Reporting group description:

Under fasted conditions a single oral dose of 300 mg lamivudine pediatric coated granules with a single oral dose of 300 mg tenofovir pediatric coated granules, with applesauce

Serious adverse events	Lamivudine 300 mg tablet + Tenofovir 300 mg tablet	Lamivudine 300 mg uncoated granules (UG) + Tenofovir 300 mg UG	Lamivudine 300 mg coated granules (CG) + Tenofovir 300 mg CG
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with pudding	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with applesauce	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with pudding
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with applesauce		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Lamivudine 300 mg tablet + Tenofovir 300 mg tablet	Lamivudine 300 mg uncoated granules (UG) + Tenofovir 300 mg UG	Lamivudine 300 mg coated granules (CG) + Tenofovir 300 mg CG
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)	3 / 23 (13.04%)	5 / 24 (20.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Head discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	2 / 24 (8.33%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	2	0	2
Hypoaesthesia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	4 / 24 (16.67%)
occurrences (all)	1	0	4
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with pudding	Lamivudine 300 mg UG + Tenofovir 300 mg UG, with applesauce	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with pudding
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	2 / 10 (20.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Head discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 12 (0.00%) 0	 0 / 10 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 12 (0.00%) 0	 0 / 10 (0.00%) 0
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 12 (0.00%) 0	 1 / 10 (10.00%) 1
Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 12 (0.00%) 0	 0 / 10 (0.00%) 0

Non-serious adverse events	Lamivudine 300 mg CG + Tenofovir 300 mg CG, with applesauce		
Total subjects affected by non-serious adverse events subjects affected / exposed	 3 / 11 (27.27%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Nervous system disorders Head discomfort subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia	 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0		

subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0 2 / 11 (18.18%) 2		
General disorders and administration site conditions Catheter site related reaction subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		
Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all)	 0 / 11 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2016	Amendment 1: Clarifications for Test Procedures, Drug Administration, and Palatability Questions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported