Clinical trial results:
A Phase 1, Single-Dose, Cross-Over Study Evaluating the Relative Bioavailability of a Pediatric Oral Granule Formulation of Tenofovir Alafenamide in Healthy Adults

Summary

EudraCT number	2019-003269-16
Trial protocol	Outside EU/EEA
Global end of trial date	19 October 2019

Results information

Result version number	v1 (current)
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-320-1196

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001584-PIP01-13
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	19 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2019
Global end of trial reached?	Yes
Global end of trial date	19 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the relative bioavailability of a pediatric oral granule formulation of tenofovir alafenamide (TAF) relative to the adult tablet formulation in healthy participants.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	12 August 2019
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	United States: 37
Worldwide total number of subjects	37
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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a study site in the United States. The first participant was screened on 12 Aug 2019. The last study visit occurred on 19 Oct 2019.

Pre-assignment

Screening details:

93 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TAF 25 mg (Treatment Sequence: Tablet- Granule)

Arm description:

Participants received single oral dose of tenofovir alafenamide (TAF) 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.

Arm type	Experimental
Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg administered on Day 1 in treatment period 1.

Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

25 mg administered on Day 13 in treatment period 2.

Arm title	TAF 25 mg (Treatment Sequence: Granule-Tablet)

Arm description:

Participants received single oral dose of TAF 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of TAF 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.

Arm type	Experimental
Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

25 mg administered on Day 1 in treatment period 1.

Investigational medicinal product name	Tenofovir alafenamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg administered on Day 13 in treatment period 2.

Number of subjects in period 1	TAF 25 mg (Treatment Sequence: Tablet-Granule)	TAF 25 mg (Treatment Sequence: Granule-Tablet)
Started	18	19
Completed	18	18
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TAF 25 mg (Treatment Sequence: Tablet- Granule)
Reporting group description:	
Participants received single oral dose of tenofovir alafenamide (TAF) 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.	
Reporting group title	TAF 25 mg (Treatment Sequence: Granule-Tablet)
Reporting group description:	
Participants received single oral dose of TAF 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of TAF 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.	

Reporting group values	TAF 25 mg (Treatment Sequence: Tablet-Granule)	TAF 25 mg (Treatment Sequence: Granule-Tablet)	Total
Number of subjects	18	19	37
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	32	34	
standard deviation	± 6.5	± 6.3	-
Gender categorical			
Units: Subjects			
Female	8	6	14
Male	10	13	23

End points

End points reporting groups

Reporting group title	TAF 25 mg (Treatment Sequence: Tablet- Granule)

Reporting group description:

Participants received single oral dose of tenofovir alafenamide (TAF) 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.

Reporting group title	TAF 25 mg (Treatment Sequence: Granule-Tablet)

Reporting group description:

Participants received single oral dose of TAF 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 1 in treatment period 1 followed by single oral dose of TAF 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 13 in treatment period 2. Each treatment period was separated by a washout period of 11 days.

Subject analysis set title	TAF Tablet
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received single oral dose of TAF 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 1 in treatment period 1 or on Day 13 in treatment period 2.

Subject analysis set title	TAF Granule
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received single oral dose of TAF 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 1 in treatment period 1 or on Day 13 in treatment period 2.

Primary: Pharmacokinetic (PK) Parameter: AUClast of TAF and its Metabolite tenofovir (TFV)

End point title	Pharmacokinetic (PK) Parameter: AUClast of TAF and its Metabolite tenofovir (TFV)

End point description:

AUClast is defined as the concentration of drug from time zero to the last observable concentration. Participants in the PK Analysis Set (included all randomized participants who took at least 1 dose of study drug and had at least 1 non-missing concentration value reported by the PK laboratory for each respective analyte) with available data were analysed.

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose on Day 1 and Day 13

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: hours*nanograms per milliter (h*ng/mL)				
arithmetic mean (standard deviation)				
TAF	196.9 (± 71.30)	208.9 (± 55.77)		
TFV	226.3 (± 33.48)	235.4 (± 38.52)		

Statistical analyses

Statistical analysis title	TAF: TAF Tablet vs TAF Granule
Statistical analysis description:	
Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.	
Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	109.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	100.93
upper limit	119.45

Statistical analysis title	TFV: TAF Tablet vs TAF Granule
Statistical analysis description:	
Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.	
Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	104.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	100.34
upper limit	108

Primary: PK Parameter: AUCinf of TAF and its Metabolite TFV	
End point title	PK Parameter: AUCinf of TAF and its Metabolite TFV
End point description:	
AUCinf is defined as the concentration of drug extrapolated to infinite time. Participants in the PK Analysis Set with the available data were analyzed.	
End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose on Day 1 and Day 13

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
TAF	198.8 (± 70.71)	211.7 (± 55.14)		
TFV	260.8 (± 38.04)	270.7 (± 43.05)		

Statistical analyses

Statistical analysis title	TAF: TAF Tablet vs TAF Granule

Statistical analysis description:

Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.

Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	109.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	101.28
upper limit	119.45

Statistical analysis title	TFV: TAF Tablet vs TAF Granule

Statistical analysis description:

Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.

Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	103.91

Confidence interval	
level	90 %
sides	2-sided
lower limit	100.25
upper limit	107.71

Primary: PK Parameter: Cmax of TAF and its Metabolite TFV

End point title	PK Parameter: Cmax of TAF and its Metabolite TFV

End point description:

Cmax is defined as the maximum concentration of drug. Participants in the PK Analysis Set with the available data were analyzed.

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose on Day 1 and Day 13

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: nanograms/milliliters (ng/mL)				
arithmetic mean (standard deviation)				
TAF	151.2 (± 96.52)	125.4 (± 46.97)		
TFV	6.3 (± 1.13)	6.1 (± 0.99)		

Statistical analyses

Statistical analysis title	TAF: TAF Tablet vs TAF Granule

Statistical analysis description:

Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.

Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	95.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	80.83
upper limit	112.24

Statistical analysis title	TFV: TAF Tablet vs TAF Granule
Statistical analysis description:	
Subjects included in this analysis states 73; however, only 37 unique participants were analyzed for Treatment TAF Tablet and Treatment TAF Granule.	
Comparison groups	TAF Tablet v TAF Granule
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	% Geometric Least Square Mean Ratio
Point estimate	97.54
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.59
upper limit	102.77

Secondary: PK Parameter: Tmax of TAF and its Metabolite TFV

End point title	PK Parameter: Tmax of TAF and its Metabolite TFV
End point description:	
Tmax is defined as the time (observed time point) of Cmax. Participants in the PK Analysis Set with the available data were analyzed.	
End point type	Secondary
End point timeframe:	
Predose (≤ 5 minutes), 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose on Day 1 and Day 13	

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: hours				
median (full range (min-max))				
TAF	1.25 (0.50 to 4.00)	1.00 (0.25 to 3.00)		
TFV	3.00 (1.50 to 6.00)	3.00 (1.50 to 5.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: t1/2 of TAF and its Metabolite TFV

End point title	PK Parameter: t1/2 of TAF and its Metabolite TFV

End point description:

t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the PK Analysis Set with the available data were analyzed.

End point type	Secondary

End point timeframe:

Predose (≤5 minutes), 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours postdose on Day 1 and Day 13

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: hours				
arithmetic mean (standard deviation)				
TAF	0.54 (± 0.252)	0.69 (± 0.318)		
TFV	51.84 (± 9.305)	51.33 (± 10.248)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events

End point description:

Participants in the Safety Analysis Set (included all randomized participants who took at least 1 dose of study drug) with available data were analyzed.

End point type	Secondary

End point timeframe:

From first dose up to Day 13 plus 30 days

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: percentage of participants				
number (not applicable)	11.1	24.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Treatment Emergent Laboratory Abnormalities

End point title	Percentage of Participants Experiencing Treatment Emergent Laboratory Abnormalities

End point description:

Treatment-emergent laboratory abnormalities were defined as values that increase at least one toxicity grade from baseline. The most severe graded abnormality from all tests was counted for each participant. Participants in the Safety Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

From first dose up to Day 13 plus 30 days

End point values	TAF Tablet	TAF Granule		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	37		
Units: percentage of participants				
number (not applicable)				
Any Grade 1 or above	33.3	24.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose up to Day 13 plus 30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	TAF Tablet
Reporting group description:	
Participants who received single oral dose of TAF 25 mg adult tablet (1 X 25 mg) under fed conditions on Day 1 in treatment period 1 or on Day 13 in treatment period 2 were analyzed.	
Reporting group title	TAF Granule
Reporting group description:	
Participants who received single oral dose of TAF 25 mg pediatric granule formulation (2 X 12.5 mg) under fed conditions on Day 1 in treatment period 1 or on Day 13 in treatment period 2 were analyzed.	

Serious adverse events	TAF Tablet	TAF Granule	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TAF Tablet	TAF Granule	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	4 / 37 (10.81%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 36 (5.56%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Somnolence			
subjects affected / exposed	0 / 36 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported