Clinical trial results:
A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Women at High Risk for HIV-1 Infection

Summary

EudraCT number	2021-001289-39
Trial protocol	Outside EU/EEA
Global end of trial date	11 June 2024

Results information

Result version number	v1 (current)
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	MK-8591-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04644029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, 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-002938-PIP01-20
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	11 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2023
Global end of trial reached?	Yes
Global end of trial date	11 June 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study evaluated whether oral islatravir (ISL) is effective in preventing Human Immunodeficiency Virus Type 1 (HIV-1) infection in women at high-risk for HIV-1 infection. The study compared oral ISL taken once a month versus standard-of-care medication for prevention of HIV-1 infection, emtricitabine/tenofovir disoproxil (FTC/TDF) taken once per day. The primary hypothesis is that oral ISL is more effective than FTC/TDF at reducing the incidence rate per year of confirmed HIV-1 infections.

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.

The following additional measure defined for this individual study was in place for the protection of trial subjects:
Based on laboratory findings of decreased lymphocyte and CD4+ T-cell counts across the islatravir program, dosing of blinded study intervention was halted on 13-Dec-2021 and screening and randomization of new participants was ended. Blinded assessments conducted prior to this date are designated as Study Part 1. During Study Part 2, participants from Part 1 have the option to receive daily open-label FTC/TDF while continuing in the study for safety monitoring. Study Part 3 was added to unblind each participant's Part 1 study intervention assignment, continue participants on FTC/TDF, and monitor safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 656
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	730
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	730
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One person mistakenly received study drug without being randomized. They are not included in Participant Flow or Baseline Characteristics because they were not enrolled in the study, but their adverse events are reported in the Adverse Events module because they received study drug.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ISL QM

Arm description:

ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Arm type	Experimental
Investigational medicinal product name	Placebo to FTC/TDF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0 mg tablet administered once daily during Part 1.

Investigational medicinal product name	Islatravir
Investigational medicinal product code	
Other name	MK-8591
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral 60 mg tablet administered once monthly during Part 1.

Arm title	FTC/TDF QD

Arm description:

FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Arm type	Active comparator
Investigational medicinal product name	Placebo to ISL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0 mg tablet administered orally once monthly in Part 1.

Investigational medicinal product name	FTC/TDF
Investigational medicinal product code	
Other name	TRUVADA™ Emtricitabine/Tenofovir disoproxil Emtricitabine/Tenofovir disoproxil fumarate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contains 200 mg emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg tenofovir disoproxil fumarate or 201.22 mg tenofovir disoproxil phosphate), administered orally once daily in Parts 1, 2, and 3.

Number of subjects in period 1	ISL QM	FTC/TDF QD
Started	364	366
Completed	362	365
Not completed	2	1
Randomized in error: not treated	2	1

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Part 1: A double-blinding technique with in-house blinding was used. Participants, investigators, and Sponsor personnel or delegates involved in study intervention administration or clinical evaluation were blinded.

Part 2: Sponsor personnel not directly involved with blinded safety monitoring were unblinded to participants' Part 1 study intervention.

Part 3: Participants, investigators, and all Sponsor personnel were unblinded to participants' original study intervention group.

Arms

Are arms mutually exclusive?	Yes
Arm title	ISL QM

Arm description:

ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Arm type	Experimental
Investigational medicinal product name	Placebo to FTC/TDF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 0 mg tablet administered once daily during Part 1.	
Investigational medicinal product name	Islatravir
Investigational medicinal product code	
Other name	MK-8591
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Oral 60 mg tablet administered once monthly during Part 1.	
Arm title	FTC/TDF QD
Arm description: FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began.	
Arm type	Active comparator
Investigational medicinal product name	Placebo to ISL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 0 mg tablet administered orally once monthly in Part 1.	
Investigational medicinal product name	FTC/TDF
Investigational medicinal product code	
Other name	TRUVADA™ Emtricitabine/Tenofovir disoproxil Emtricitabine/Tenofovir disoproxil fumarate
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Each tablet contains 200 mg emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg tenofovir disoproxil fumarate or 201.22 mg tenofovir disoproxil phosphate), administered orally once daily in Parts 1, 2, and 3.	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The All Patients as Treated population was used as the baseline population.

Number of subjects in period 2[2]	ISL QM	FTC/TDF QD
Started	362	365
Received Open-Label FTC/TDF	343	345
Completed	0	0
Not completed	362	365
Adverse event, serious fatal	1	-
Physician decision	1	2
Consent withdrawn by subject	21	19
Unknown	-	1
Study Terminated by Sponsor	308	309
Lost to follow-up	31	34

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics were calculated on the number of participants treated instead of the number randomized (worldwide total). 3 participants randomized in error and were not treated, so this "Treated" period is a more accurate representation of the population assessed throughout the study.

Baseline characteristics

Reporting groups	
Reporting group title	ISL QM
Reporting group description:	
ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF. Placebo was no longer administered once open label treatment began.	
Reporting group title	FTC/TDF QD
Reporting group description:	
FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began.	

Reporting group values	ISL QM	FTC/TDF QD	Total
Number of subjects	362	365	727
Age categorical			
The baseline characteristics population includes all randomized participants who received study drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	362	365	727
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
The baseline characteristics population includes all randomized participants who received study drug.			
Units: years			
arithmetic mean	26.0	26.1	
standard deviation	± 6.1	± 6.3	-
Sex: Female, Male			
The baseline characteristics population includes all randomized participants who received study drug.			
Units: Participants			
Female	362	365	727
Male	0	0	0
Race (NIH/OMB)			
The baseline characteristics population includes all randomized participants who received study drug.			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	5	6	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	334	338	672
White	19	15	34
More than one race	3	4	7

Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			
The baseline characteristics population includes all randomized participants who received study drug.			
Units: Subjects			
Hispanic or Latino	11	13	24
Not Hispanic or Latino	329	330	659
Unknown or Not Reported	22	22	44

End points

End points reporting groups

Reporting group title	ISL QM

Reporting group description:

ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Reporting group title	FTC/TDF QD

Reporting group description:

FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Reporting group title	ISL QM

Reporting group description:

ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Reporting group title	FTC/TDF QD

Reporting group description:

FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began.

Primary: Incidence Rate Per Year of Confirmed HIV-1 infection Among Participants During Blinded Treatment +42 Days Post-Blind

End point title	Incidence Rate Per Year of Confirmed HIV-1 infection Among Participants During Blinded Treatment +42 Days Post-Blind[1]

End point description:

Incidence rate per year of confirmed HIV-1 infections is the number of participants with confirmed HIV-1 infections during the assessment period divided by the number of person-years in the arm. Data are based on participants with confirmed HIV-1 infection. The originally planned primary statistical analysis was removed via amendment when open-label treatment was initiated. The analysis population includes all participants who were randomized and received at least 1 dose of study intervention and did not have confirmed HIV-1 infections prior to or at randomization.

End point type	Primary

End point timeframe:

Up to approximately 325 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	ISL QM	FTC/TDF QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	363		
Units: Percentage of Participants/Person-Year				
number (not applicable)	0.000	0.000		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Blinded Study Treatment Due to an AE

End point title	Number of Participants Who Discontinued Blinded Study Treatment Due to an AE[2]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who discontinued blinded study treatment due to an AE will be reported for each treatment arm. The analysis population includes all participants who were randomized and received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Up to 283 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	ISL QM	FTC/TDF QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	365		
Units: Participants	2	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced an Adverse Event (AE) During Blinded Treatment + 42 Days Post-Blind

End point title	Number of Participants Who Experienced an Adverse Event (AE) During Blinded Treatment + 42 Days Post-Blind[3]

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who experienced an AE will be reported for each treatment arm. The analysis population includes all participants who were randomized and received at least 1 dose of study intervention.

End point type	Primary

End point timeframe:

Up to approximately 325 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	ISL QM	FTC/TDF QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	365		
Units: Participants	198	255		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence Rate Per Year During Blinded Treatment of Confirmed HIV-1 infection Among ISL-Treated Participants

End point title	Incidence Rate Per Year During Blinded Treatment of Confirmed HIV-1 infection Among ISL-Treated Participants[4]

End point description:

Incidence rate per year of confirmed HIV-1 infections is the number of participants with confirmed HIV-1 infections during the assessment period divided by the number of person-years in the arm. Data are based on participants with confirmed HIV-1 infection. The originally planned secondary statistical analysis was removed via amendment when open-label treatment was initiated. The analysis population includes all participants who were randomized and received at least 1 dose of ISL and did not have confirmed HIV-1 infections prior to or at randomization.

End point type	Secondary

End point timeframe:

Up to approximately 237 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, data are only presented for the ISL-treated arm.

End point values	ISL QM			
Subject group type	Reporting group			
Number of subjects analysed	362			
Units: Percentage of Participants/Person-Year				
number (not applicable)	0.000			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Blinded arms and mistaken treatment arm: Up to approximately 325 days
Open-label arms: Up to approximately 866 days (starting 42 days after last blinded treatment; includes the time leading up to first open-label treatment)

Adverse event reporting additional description:

Following sponsor decision to stop dosing blinded study treatment, participants were offered the option to receive open-label FTC/TDF. Open-label arms include all events occurring >42 days after a participant's final blinded treatment.
All-Cause Mortality includes all randomized participants starting from the time of randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	FTC/TDF QD

Reporting group description:

FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily. Placebo to ISL (islatravir) administered once monthly. Following study-wide cessation of ISL administration, participants had the option to continue on open-label FTC/TDF. Placebo was no longer administered once open label treatment began. Adverse events during the open-label period are not counted in this arm.

Reporting group title	ISL QM

Reporting group description:

ISL (islatravir) once monthly AND placebo to FTC/TDF (emtricitabine/tenofovir disoproxil) once daily. Following study-wide cessation of ISL administration, participants had the option to receive open-label FTC/TDF administered once daily. Adverse events during the open-label period are not counted in this arm.

Reporting group title	FTC/TDF > Open-Label FTC/TDF Second Course

Reporting group description:

This arm represents participants who received open-label FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily, after previously receiving FTC/TDF QD during the blinded portion of the study.

Reporting group title	FTC/TDF-Treated Without Randomization

Reporting group description:

The participant in this arm was mistakenly given daily FTC/TDF plus monthly placebo to ISL without completing enrollment and randomization. Following study unblinding, participant continued to receive open-label daily FTC/TDF. Adverse events were collected for this participant during blinded and open-label treatment due to receiving study drug, but zero participants are reported as affected and zero adverse event instances are reported due to the risk of identification of a person.

Reporting group title	ISL QM > Open-Label FTC/TDF

Reporting group description:

This arm represents participants who received open-label FTC/TDF (TRUVADA™ or generic product emtricitabine/tenofovir disoproxil) administered once daily, after previously receiving ISL QM during the blinded portion of the study.

Serious adverse events	FTC/TDF QD	ISL QM	FTC/TDF > Open-Label FTC/TDF Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 365 (0.55%)	4 / 362 (1.10%)	22 / 345 (6.38%)

number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crush injury			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	1 / 365 (0.27%)	0 / 362 (0.00%)	4 / 345 (1.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic pregnancy			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failed trial of labour			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gestational hypertension			

subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature rupture of membranes			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prolonged labour			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spontaneous rupture of membranes			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia of pregnancy			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 365 (0.27%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nephrolithiasis			

subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	1 / 365 (0.27%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 365 (0.00%)	1 / 362 (0.28%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal loss of weight			
subjects affected / exposed	0 / 365 (0.00%)	0 / 362 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FTC/TDF-Treated Without Randomization	ISL QM > Open-Label FTC/TDF	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	13 / 343 (3.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crush injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			

subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	0 / 1 (0.00%)	2 / 343 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failed trial of labour			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational hypertension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged labour			

subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous rupture of membranes			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia of pregnancy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Small intestinal obstruction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional self-injury			

subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 1 (0.00%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal loss of weight			
subjects affected / exposed	0 / 1 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FTC/TDF QD	ISL QM	FTC/TDF > Open-Label FTC/TDF Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 365 (57.53%)	145 / 362 (40.06%)	284 / 345 (82.32%)
Investigations			
CD4 lymphocytes decreased			
subjects affected / exposed	4 / 365 (1.10%)	4 / 362 (1.10%)	14 / 345 (4.06%)
occurrences (all)	4	4	18
Blood pressure increased			
subjects affected / exposed	4 / 365 (1.10%)	2 / 362 (0.55%)	18 / 345 (5.22%)
occurrences (all)	5	2	21
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 365 (0.82%)	1 / 362 (0.28%)	10 / 345 (2.90%)
occurrences (all)	3	1	11
Blood bicarbonate decreased			
subjects affected / exposed	1 / 365 (0.27%)	0 / 362 (0.00%)	21 / 345 (6.09%)
occurrences (all)	1	0	25
Creatinine renal clearance decreased			
subjects affected / exposed	4 / 365 (1.10%)	1 / 362 (0.28%)	20 / 345 (5.80%)
occurrences (all)	4	1	32

Nervous system disorders			
Headache			
subjects affected / exposed	53 / 365 (14.52%)	43 / 362 (11.88%)	56 / 345 (16.23%)
occurrences (all)	65	50	83
Dizziness			
subjects affected / exposed	27 / 365 (7.40%)	17 / 362 (4.70%)	3 / 345 (0.87%)
occurrences (all)	28	17	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 365 (5.21%)	10 / 362 (2.76%)	5 / 345 (1.45%)
occurrences (all)	19	12	5
Influenza like illness			
subjects affected / exposed	3 / 365 (0.82%)	4 / 362 (1.10%)	41 / 345 (11.88%)
occurrences (all)	3	4	62
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	41 / 365 (11.23%)	19 / 362 (5.25%)	13 / 345 (3.77%)
occurrences (all)	43	21	15
Diarrhoea			
subjects affected / exposed	29 / 365 (7.95%)	19 / 362 (5.25%)	21 / 345 (6.09%)
occurrences (all)	32	19	23
Vomiting			
subjects affected / exposed	22 / 365 (6.03%)	8 / 362 (2.21%)	12 / 345 (3.48%)
occurrences (all)	25	9	13
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	11 / 365 (3.01%)	13 / 362 (3.59%)	39 / 345 (11.30%)
occurrences (all)	15	16	53
Vaginal discharge			
subjects affected / exposed	11 / 365 (3.01%)	7 / 362 (1.93%)	30 / 345 (8.70%)
occurrences (all)	12	7	38
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 365 (2.19%)	11 / 362 (3.04%)	25 / 345 (7.25%)
occurrences (all)	8	11	28
Infections and infestations			

Trichomoniasis			
subjects affected / exposed	11 / 365 (3.01%)	2 / 362 (0.55%)	24 / 345 (6.96%)
occurrences (all)	12	2	28
Upper respiratory tract infection			
subjects affected / exposed	12 / 365 (3.29%)	21 / 362 (5.80%)	55 / 345 (15.94%)
occurrences (all)	13	24	74
Gastroenteritis			
subjects affected / exposed	6 / 365 (1.64%)	7 / 362 (1.93%)	18 / 345 (5.22%)
occurrences (all)	6	7	18
Chlamydial infection			
subjects affected / exposed	17 / 365 (4.66%)	4 / 362 (1.10%)	55 / 345 (15.94%)
occurrences (all)	17	4	71
Bacterial vaginosis			
subjects affected / exposed	57 / 365 (15.62%)	28 / 362 (7.73%)	143 / 345 (41.45%)
occurrences (all)	59	30	255
Urinary tract infection			
subjects affected / exposed	5 / 365 (1.37%)	0 / 362 (0.00%)	34 / 345 (9.86%)
occurrences (all)	5	0	38
Vulvovaginal candidiasis			
subjects affected / exposed	29 / 365 (7.95%)	13 / 362 (3.59%)	109 / 345 (31.59%)
occurrences (all)	30	13	160

Non-serious adverse events	FTC/TDF-Treated Without Randomization	ISL QM > Open-Label FTC/TDF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	292 / 343 (85.13%)	
Investigations			
CD4 lymphocytes decreased			
subjects affected / exposed	0 / 1 (0.00%)	18 / 343 (5.25%)	
occurrences (all)	0	24	
Blood pressure increased			
subjects affected / exposed	0 / 1 (0.00%)	21 / 343 (6.12%)	
occurrences (all)	0	28	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1 (0.00%)	19 / 343 (5.54%)	
occurrences (all)	0	20	
Blood bicarbonate decreased			

subjects affected / exposed	0 / 1 (0.00%)	17 / 343 (4.96%)	
occurrences (all)	0	22	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 1 (0.00%)	26 / 343 (7.58%)	
occurrences (all)	0	36	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 1 (0.00%)	61 / 343 (17.78%)	
occurrences (all)	0	90	
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	11 / 343 (3.21%)	
occurrences (all)	0	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	5 / 343 (1.46%)	
occurrences (all)	0	8	
Influenza like illness			
subjects affected / exposed	0 / 1 (0.00%)	45 / 343 (13.12%)	
occurrences (all)	0	65	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	13 / 343 (3.79%)	
occurrences (all)	0	16	
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	14 / 343 (4.08%)	
occurrences (all)	0	16	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	15 / 343 (4.37%)	
occurrences (all)	0	17	
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 1 (0.00%)	33 / 343 (9.62%)	
occurrences (all)	0	42	
Vaginal discharge			
subjects affected / exposed	0 / 1 (0.00%)	30 / 343 (8.75%)	
occurrences (all)	0	36	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	16 / 343 (4.66%)	
occurrences (all)	0	19	
Infections and infestations			
Trichomoniasis			
subjects affected / exposed	0 / 1 (0.00%)	28 / 343 (8.16%)	
occurrences (all)	0	36	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	70 / 343 (20.41%)	
occurrences (all)	0	89	
Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)	16 / 343 (4.66%)	
occurrences (all)	0	18	
Chlamydial infection			
subjects affected / exposed	0 / 1 (0.00%)	58 / 343 (16.91%)	
occurrences (all)	0	78	
Bacterial vaginosis			
subjects affected / exposed	0 / 1 (0.00%)	158 / 343 (46.06%)	
occurrences (all)	0	263	
Urinary tract infection			
subjects affected / exposed	0 / 1 (0.00%)	31 / 343 (9.04%)	
occurrences (all)	0	38	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 1 (0.00%)	114 / 343 (33.24%)	
occurrences (all)	0	163	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2021	Amendment 1: Modified the management of participants who become pregnant, modified PK assessments for participants who become pregnant and remain on ISL, and modified breastfeeding options for participants who become pregnant.
07 December 2021	Amendment 2: Increased frequency of monitoring of lymphocytes, added monitoring of CD4+ T-cells, and added discontinuation criteria in response to findings of decreases in lymphocytes (in studies of participants with or without HIV) and CD4+ T-cell counts (in studies of participants with HIV) in ISL clinical studies.
01 March 2022	Amendment 3: Defined changes in study design and conduct implemented due to stopping of blinded study intervention, and to describe continued monitoring of participants, as a result of the 13-Dec-2021 discontinuation of blinded study intervention and consequent treatment changes.
29 June 2022	Amendment 4: Added Part 3 to the study to unblind each participant's Part 1 study intervention assignment, continue participants on FTC/TDF, and monitor safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 June 2024	This is date of study termination after adequate follow-up with infants born to participants enrolled in the study.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Based on laboratory findings of decreased lymphocyte and CD4+ T-cell counts across the islatravir program, dosing of blinded study intervention was halted on 13-Dec-2021 and screening and randomization of new participants was ended.

Notes: