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 Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection

Summary

EudraCT number	2020-003309-79
Trial protocol	FR Outside EU/EEA
Global end of trial date	04 August 2023

Results information

Result version number	v1
This version publication date	14 February 2024
First version publication date	14 February 2024

Trial information

Trial identification

Sponsor protocol code	MK-8591-024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04652700
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	04 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2023
Global end of trial reached?	Yes
Global end of trial date	04 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and tolerability of oral Islatravir (ISL) once monthly (QM) as Preexposure Prophylaxis (PrEP) in cisgender men who have sex with men and transgender women who have sex with men and who are at high risk of HIV-1 infection with 48 or 96 weeks of treatment and a follow-up of ≥42 days.

Due to decreased lymphocyte and CD4+ T-cell counts across the ISL program, blinded dosing was halted on 10-Dec-2021, with no further enrollment. Thus, no participants <18 years of age were randomized. Assessments conducted prior to then are designated as Part 1. In Part 2, participants from Part 1 were switched to open-label PrEP therapy with emtricitabine/tenofovir disoproxil (FTC/TDF) or emtricitabine/tenofovir alafenamide (FTC/TAF) while continuing in the study. In Part 3, the study was unblinded to original randomized intervention group, and participants were permitted to continue receiving unblinded FTC/TDF or FTC/TAF until the end of the study.

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	15 March 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	France: 12
Country: Number of subjects enrolled	Japan: 26
Country: Number of subjects enrolled	South Africa: 59
Country: Number of subjects enrolled	Thailand: 68
Country: Number of subjects enrolled	United States: 277
Country: Number of subjects enrolled	Peru: 52
Worldwide total number of subjects	494
EEA total number of subjects	12

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)	492
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized at 23 study sites in France, Japan, Peru, South Africa, and the United States.

Period 1

Period 1 title	Main Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ISL QM Group

Arm description:

Participants received 60 mg tablet of ISL QM monthly (QM) plus placebo to FTC/TDF tablet once daily (QD) or placebo to FTC/TAF tablet QD for up to 24 months of treatment duration.

Arm type	Experimental
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:

ISL 60 mg tablet, QM, orally for up to 24 months

Investigational medicinal product name	Placebo to FTC/TAF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo FTC/TAF 0 mg tablets QD, orally for up to 24 months

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:

Placebo FTC/TDF 0 mg tablets QD, orally for up to 24 months

Arm title	FTC/TDF or FTC/TAF QD Group

Arm description:

Participants receive 200/245 mg or 200/300 mg of FTC/TDF combination tablet, QD, orally or 200/25 mg of FTC/TAF combination tablet, QD, orally at investigator's discretion plus Placebo to ISL tablet QM, orally for up to 24 months of treatment duration.

Arm type	Active comparator

Investigational medicinal product name	Emtricitabine/Tenofovir Disoproxil Fumarate
Investigational medicinal product code	
Other name	FTC/TDF Truvada
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants receive 200/245 mg of FTC/TDF combination tablet, QD, orally for up to 24 months

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:

Placebo ISL 0 mg tablets QM, orally for up to 24 months

Investigational medicinal product name	Emtricitabine/Tenofovir Alafenamide
Investigational medicinal product code	
Other name	Descovy
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants receive 200/25 mg of FTC/TAF combination tablet, QD, orally for up to 24 months

Number of subjects in period 1	ISL QM Group	FTC/TDF or FTC/TAF QD Group
Started	328	166
Completed	0	0
Not completed	328	166
Physician decision	1	2
Consent withdrawn by subject	52	29
Not reported	2	1
Lost to follow-up	51	15
Study terminated by Sponsor.	222	119

Baseline characteristics

Reporting groups	
Reporting group title	ISL QM Group
Reporting group description:	
Participants received 60 mg tablet of ISL QM monthly (QM) plus placebo to FTC/TDF tablet once daily (QD) or placebo to FTC/TAF tablet QD for up to 24 months of treatment duration.	
Reporting group title	FTC/TDF or FTC/TAF QD Group
Reporting group description:	
Participants receive 200/245 mg or 200/300 mg of FTC/TDF combination tablet, QD, orally or 200/25 mg of FTC/TAF combination tablet, QD, orally at investigator's discretion plus Placebo to ISL tablet QM, orally for up to 24 months of treatment duration.	

Reporting group values	ISL QM Group	FTC/TDF or FTC/TAF QD Group	Total
Number of subjects	328	166	494
Age Categorical 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)	327	165	492
From 65-84 years	1	1	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	29.6	29.5	
standard deviation	± 9.6	± 9.2	-
Gender Categorical Units: Subjects			
Female	0	0	0
Male	328	166	494
Race Units: Subjects			
American Indian Or Alaska Native	2	0	2
Asian	70	31	101
Black Or African American	83	41	124
Multiple	35	20	55
Native Hawaiian Or Other Pacific Islander	2	0	2
White	135	71	206
Missing	1	3	4
Ethnicity Units: Subjects			
Hispanic Or Latino	111	51	162
Not Hispanic Or Latino	214	111	325

Not Reported	3	4	7

End points

End points reporting groups

Reporting group title	ISL QM Group
Reporting group description:	
Participants received 60 mg tablet of ISL QM monthly (QM) plus placebo to FTC/TDF tablet once daily (QD) or placebo to FTC/TAF tablet QD for up to 24 months of treatment duration.	
Reporting group title	FTC/TDF or FTC/TAF QD Group
Reporting group description:	
Participants receive 200/245 mg or 200/300 mg of FTC/TDF combination tablet, QD, orally or 200/25 mg of FTC/TAF combination tablet, QD, orally at investigator's discretion plus Placebo to ISL tablet QM, orally for up to 24 months of treatment duration.	

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[1]
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.	
End point type	Primary
End point timeframe:	
Up to approximately 12 months	

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: Per protocol, only descriptive statistics are presented.

End point values	ISL QM Group	FTC/TDF or FTC/TAF QD Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	166		
Units: Participants	211	128		

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 experienced an AE will be reported for each treatment arm.	
End point type	Primary

End point timeframe:

Up to approximately 10 months

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: Per protocol, only descriptive statistics are presented.

End point values	ISL QM Group	FTC/TDF or FTC/TAF QD Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	166		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Incidence Rate Per Year During Blinded Treatment of Confirmed HIV-1 infection Among Participants

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. Data are based on participants with confirmed HIV-1 infection.

End point type	Secondary

End point timeframe:

Up to approximately 12 months

End point values	ISL QM Group	FTC/TDF or FTC/TAF QD Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	166		
Units: Number of Participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study: Blinded Treatment + Open-Label Standard-of-Care Treatment (Up to approximately 26 months)

Adverse event reporting additional description:

All treated participants are included. Data are presented according the initial randomized Blinded Treatment, but include events during the Blinded Treatment and Open-Label Standard-of-Care Periods.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	FTC/TDF or FTC/TAF QD Group

Reporting group description:

Participants receive 200/245 mg or 200/300 mg of FTC/TDF combination tablet, QD, orally or 200/25 mg of FTC/TAF combination tablet, QD, orally at investigator's discretion plus Placebo to ISL tablet QM, orally for up to 24 months of treatment duration.

Reporting group title	ISL QM Group

Reporting group description:

Participants receive 60 mg tablet of ISL QM, orally plus placebo to FTC/TDF tablet QD or placebo to FTC/TAF tablet QD, orally for up to 24 months of treatment duration.

Serious adverse events	FTC/TDF or FTC/TAF QD Group	ISL QM Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 166 (3.61%)	21 / 328 (6.40%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Proctitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	2 / 166 (1.20%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 166 (1.20%)	9 / 328 (2.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 166 (0.60%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
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 or FTC/TAF QD Group	ISL QM Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	136 / 166 (81.93%)	276 / 328 (84.15%)	
Investigations			
CD4 lymphocytes decreased			
subjects affected / exposed	8 / 166 (4.82%)	24 / 328 (7.32%)	
occurrences (all)	13	30	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 166 (9.64%)	28 / 328 (8.54%)	
occurrences (all)	22	37	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 166 (4.82%)	20 / 328 (6.10%)	
occurrences (all)	13	23	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 166 (11.45%)	32 / 328 (9.76%)	
occurrences (all)	22	22	
Haemorrhoids			

subjects affected / exposed	10 / 166 (6.02%)	14 / 328 (4.27%)	
occurrences (all)	11	15	
Nausea			
subjects affected / exposed	11 / 166 (6.63%)	15 / 328 (4.57%)	
occurrences (all)	11	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 166 (4.82%)	21 / 328 (6.40%)	
occurrences (all)	8	22	
Oropharyngeal pain			
subjects affected / exposed	16 / 166 (9.64%)	19 / 328 (5.79%)	
occurrences (all)	18	21	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 166 (7.83%)	19 / 328 (5.79%)	
occurrences (all)	15	20	
Back pain			
subjects affected / exposed	10 / 166 (6.02%)	12 / 328 (3.66%)	
occurrences (all)	13	13	
Infections and infestations			
COVID-19			
subjects affected / exposed	58 / 166 (34.94%)	107 / 328 (32.62%)	
occurrences (all)	62	115	
Chlamydial infection			
subjects affected / exposed	9 / 166 (5.42%)	17 / 328 (5.18%)	
occurrences (all)	11	19	
Gastroenteritis			
subjects affected / exposed	9 / 166 (5.42%)	11 / 328 (3.35%)	
occurrences (all)	10	12	
Influenza			
subjects affected / exposed	20 / 166 (12.05%)	16 / 328 (4.88%)	
occurrences (all)	22	25	
Latent syphilis			
subjects affected / exposed	3 / 166 (1.81%)	19 / 328 (5.79%)	
occurrences (all)	3	24	
Nasopharyngitis			

subjects affected / exposed	17 / 166 (10.24%)	38 / 328 (11.59%)	
occurrences (all)	20	47	
Oropharyngeal gonococcal infection			
subjects affected / exposed	32 / 166 (19.28%)	51 / 328 (15.55%)	
occurrences (all)	40	73	
Pharyngeal chlamydia infection			
subjects affected / exposed	3 / 166 (1.81%)	20 / 328 (6.10%)	
occurrences (all)	3	20	
Proctitis chlamydial			
subjects affected / exposed	34 / 166 (20.48%)	78 / 328 (23.78%)	
occurrences (all)	51	106	
Proctitis gonococcal			
subjects affected / exposed	40 / 166 (24.10%)	59 / 328 (17.99%)	
occurrences (all)	57	77	
Syphilis			
subjects affected / exposed	21 / 166 (12.65%)	25 / 328 (7.62%)	
occurrences (all)	22	30	
Upper respiratory tract infection			
subjects affected / exposed	24 / 166 (14.46%)	39 / 328 (11.89%)	
occurrences (all)	28	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2021	AM1: The purpose of this amendment was to update the statistical methods for primary and secondary objectives.
06 December 2021	AM2: The purpose of this amendment was to increase frequency of monitoring of lymphocytes and to add C4+ T-cell monitoring.
24 February 2022	AM3: The purpose of this amendment was to halt dosing of blinded study intervention and to give participants the option to receive daily FTC/TDF or FTC/TAF.
03 August 2022	AM4: The purpose of this amendment was to add Part 3 to unblind each participant's Part 1 study intervention and monitor safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 December 2021	Dosing of blinded study intervention was halted on 10-Dec-2021 due to findings of decreased lymphocyte and CD4+ T-cell counts.	-

Notes:

Limitations and caveats

None reported