Clinical trial results:
A Phase 2 Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Doravirine/Islatravir in Pediatric Participants with HIV-1 Infection who are Virologically Suppressed or Treatment-Naïve, are Less Than 18 Years of Age, and Weigh Greater Than or Equal to 35 kg

Summary

EudraCT number	2019-003597-10
Trial protocol	IT Outside EU/EEA
Global end of trial date	25 January 2023

Results information

Result version number	v1 (current)
This version publication date	02 August 2023
First version publication date	02 August 2023

Trial information

Trial identification

Sponsor protocol code	MK-8591A-028

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04295772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, 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-002707-PIP19-01
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 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2021
Global end of trial reached?	Yes
Global end of trial date	25 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase 2, single-group, multi-site, open-label study of a doravirine/islatravir 100 mg/0.75 mg (DOR/ISL, MK-8591A) fixed dose combination (FDC) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric participants who are virologically suppressed (VS) on antiretroviral therapy (ART) for ≥3 months or are treatment-naive (TN). The primary purposes of the study are 1) to examine the steady-state pharmacokinetics (PK) of ISL in plasma; 2) the steady-state PK of ISL-triphosphate (ISL-TP) in peripheral blood mononuclear cells (PBMCs); and 3) to examine the safety and tolerability of DOR/ISL (100 mg/0.75 mg).

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	26 November 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	40
EEA total number of subjects	3

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)	3
Adolescents (12-17 years)	35
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Pediatric participants who were ≥35 kg body weight and <18 years of age were recruited at 18 study sites located in Italy, Russian Federation, Thailand, South Africa, and the United States. Two VS participants are excluded from results due to a consent issue.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DOR/ISL: Virologically Suppressed Cohort

Arm description:

VS participants (had taken stable 2- or 3-drug combination ART for ≥3 months) pediatric participants with HIV-1 infection receive DOR/ISL for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	DOR/ISL
Investigational medicinal product code	MK-8591A
Other name	Doravirine/islatravir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg DOR/0.75 mg ISL FDC tablet taken once daily by mouth.

Arm title	DOR/ISL: Treatment Naive Cohort

Arm description:

TN participants with HIV-1 infection receive DOR/ISL for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	DOR/ISL
Investigational medicinal product code	MK-8591A
Other name	Doravirine/islatravir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg DOR/0.75 mg ISL FDC tablet taken once daily by mouth.

Number of subjects in period 1	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort
Started	37	3
Completed	22	2
Not completed	15	1
Ongoing for safety monitoring	14	1

Protocol deviation	1	-

Period 2

Period 2 title	Extended Follow-Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring

Arm description:

A subset of VS participants who completed the study opted to participate in an extended safety monitoring period.

Arm type	Safety Monitoring

No investigational medicinal product assigned in this arm

Arm title	DOR/ISL: Treatment Naive Cohort: Extended Monitoring

Arm description:

A TN participant who completed the study opted to participate in an extended safety monitoring period.

Arm type	Safety Monitoring

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring	DOR/ISL: Treatment Naive Cohort: Extended Monitoring
Started	14	1
Completed	14	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A subset of participants who completed the main study opted to participate in an extended monitoring period.

Baseline characteristics

Reporting groups	
Reporting group title	DOR/ISL: Virologically Suppressed Cohort
Reporting group description: VS participants (had taken stable 2- or 3-drug combination ART for ≥3 months) pediatric participants with HIV-1 infection receive DOR/ISL for 96 weeks.	
Reporting group title	DOR/ISL: Treatment Naive Cohort
Reporting group description: TN participants with HIV-1 infection receive DOR/ISL for 96 weeks.	

Reporting group values	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort	Total
Number of subjects	37	3	40
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)	3	0	3
Adolescents (12-17 years)	32	3	35
Adults (18-64 years)	2	0	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	14.7	15.7	
standard deviation	± 2.2	± 1.5	-
Sex: Female, Male Units: participants			
Female	14	1	15
Male	23	2	25
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	3	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	20	0	20
White	8	0	8
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	35	3	38
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	DOR/ISL: Virologically Suppressed Cohort
Reporting group description:	
VS participants (had taken stable 2- or 3-drug combination ART for ≥3 months) pediatric participants with HIV-1 infection receive DOR/ISL for 96 weeks.	
Reporting group title	DOR/ISL: Treatment Naive Cohort
Reporting group description:	
TN participants with HIV-1 infection receive DOR/ISL for 96 weeks.	
Reporting group title	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring
Reporting group description:	
A subset of VS participants who completed the study opted to participate in an extended safety monitoring period.	
Reporting group title	DOR/ISL: Treatment Naive Cohort: Extended Monitoring
Reporting group description:	
A TN participant who completed the study opted to participate in an extended safety monitoring period.	

Primary: Maximum plasma concentration (Cmax) of ISL 0.75 mg

End point title	Maximum plasma concentration (Cmax) of ISL 0.75 mg[1][2]
End point description:	
The Cmax of ISL 0.75 mg in plasma was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.	
End point type	Primary
End point timeframe:	
Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28	

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.

[2] - 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, only descriptive statistics are presented.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: µmol/L				
geometric mean (geometric coefficient of variation)	0.0245 (± 53.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the plasma drug concentration-time curve from 0 to 24 hours post-dose (AUC0-24) of islatravir (ISL) 0.75 mg

End point title	Area under the plasma drug concentration-time curve from 0 to 24 hours post-dose (AUC0-24) of islatravir (ISL) 0.75 mg[3][4]

End point description:

The AUC0-24 of ISL 0.75 mg in plasma was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28

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: Per protocol, only descriptive statistics are presented.

[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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hr*µmol/L				
geometric mean (geometric coefficient of variation)	0.114 (± 28.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to reach maximum plasma concentration (Tmax) of ISL 0.75 mg

End point title	Time to reach maximum plasma concentration (Tmax) of ISL 0.75 mg[5][6]

End point description:

The Tmax of ISL 0.75 mg in plasma was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28

Notes:

[5] - 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.

[6] - 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, only descriptive statistics are presented.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (full range (min-max))	1.00 (0.50 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-last of ISL-triphosphate (ISL-TP) in Peripheral Blood Mononuclear Cells (PBMCs)

End point title	AUC0-last of ISL-triphosphate (ISL-TP) in Peripheral Blood Mononuclear Cells (PBMCs)[7][8]

End point description:

The AUC0-24 of ISL-TP in PBMCs was determined at steady state. A subset of VS participants was included in the Intensive PBMC PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on intracellular PBMC PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 4 and 24 hours post-dose on Day 28

Notes:

[7] - 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.

[8] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hr*pmol/10^6 cells				
geometric mean (geometric coefficient of variation)	52.3 (± 74.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of ISL-TP in PBMCs

End point title	Cmax of ISL-TP in PBMCs[9][10]

End point description:

The Cmax of ISL-TP in PBMCs was determined at steady state. A subset of VS participants was included in the Intensive PBMC PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on intracellular PBMC PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 4, and 24 hours post-dose on Day 28

Notes:

[9] - 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.

[10] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: pmol/10^6 cells				
geometric mean (geometric coefficient of variation)	2.87 (± 91.6)			

Statistical analyses

No statistical analyses for this end point

Primary: C24 of ISL-TP in PBMCs

End point title	C24 of ISL-TP in PBMCs[11][12]

End point description:

The C24 of ISL-TP in PBMCs was determined at steady state. A subset of VS participants was included in the Intensive PBMC PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on intracellular PBMC PK parameters.

End point type	Primary

End point timeframe:

24 hours post-dose on Day 28

Notes:

[11] - 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.

[12] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: pmol/10^6 cells				
geometric mean (geometric coefficient of variation)	2.05 (± 71.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent volume of distribution during terminal phase (Vz/F) of ISL 0.75 mg

End point title	Apparent volume of distribution during terminal phase (Vz/F) of ISL 0.75 mg[13][14]

End point description:

The Vz/F of ISL 0.75 mg was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28

Notes:

[13] - 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.

[14] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Liters				
geometric mean (geometric coefficient of variation)	536 (± 61.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent total clearance from plasma (CL/F) of ISL 0.75 mg

End point title	Apparent total clearance from plasma (CL/F) of ISL 0.75

End point description:

The CL/F of ISL 0.75 mg from plasma was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28

Notes:

[15] - 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.

[16] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: L/hr				
geometric mean (geometric coefficient of variation)	22.5 (± 28.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent plasma terminal half-life (t½) of ISL 0.75 mg

End point title	Apparent plasma terminal half-life (t½) of ISL 0.75 mg[17][18]

End point description:

The t½ of ISL 0.75 mg in plasma was determined at steady state. A subset of VS participants was included in the Intensive PK Cohort, consisting of participants who complied with the protocol sufficiently to ensure data were likely to exhibit the effects of the study intervention on plasma PK parameters.

End point type	Primary

End point timeframe:

Pre-dose, and 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 28

Notes:

[17] - 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.

[18] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
geometric mean (geometric coefficient of variation)	16.5 (± 70.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants experiencing ≥1 adverse event (AE)

End point title	Number of participants experiencing ≥1 adverse event (AE)[19]

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. All participants who received ≥1 dose of study intervention are included.

End point type	Primary

End point timeframe:

Up to 24 weeks

Notes:

[19] - 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	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants	21	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants discontinuing from study treatment due to an AE

End point title	Number of participants discontinuing from study treatment due to an AE[20]

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. All participants who received ≥1 dose of study intervention are included.

End point type	Primary

End point timeframe:

Up to 24 weeks

Notes:

[20] - 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	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CD4+ T-cells in TN participants

End point title	Change from baseline in CD4+ T-cells in TN participants[21]

End point description:

CD4+ T-cell counts were measured by a central laboratory. Negative and positive results represent a decrease and increase, respectively, from baseline CD4+ T-cell counts. TN participants who received ≥1 dose of study intervention and had baseline and Week 24 data available are included.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[21] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Treatment Naive Cohort			
Subject group type	Reporting group			
Number of subjects analysed	1[22]			
Units: cells/mm^3				
number (not applicable)	705.0			

Notes:

[22] - 95% CI were not calculable due to n=1.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of virologically suppressed (VS) participants with HIV-1 ribonucleic acid (RNA) ≥50 copies/mL

End point title	Percentage of virologically suppressed (VS) participants with HIV-1 ribonucleic acid (RNA) ≥50 copies/mL[23]

End point description:

The percentage of VS participants with HIV-1 RNA ≥50 copies/mL was determined at the central

laboratory with an Abbott Real Time Polymerase Chain Reaction (PCR) assay with a lower limit of detection (LLOD) of 40 copies/mL. Participants who were VS at baseline (on stable combination antiretroviral therapy [ART] for ≥3 months) and had data available are included.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[23] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)	2.9 (0.1 to 15.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of VS participants with HIV-1 RNA <50 copies/mL

End point title	Percentage of VS participants with HIV-1 RNA <50

End point description:

The percentage of VS participants with HIV-1 RNA <50 copies/mL will be determined at the central laboratory with an Abbott Real Time PCR assay with a LLOD of 40 copies/mL. Participants who were VS at baseline (on stable combination ART for ≥3 months) and had data available are included.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[24] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)	94.1 (80.3 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of treatment naive (TN) participants with HIV-1 RNA <50 copies/mL

End point title	Percentage of treatment naive (TN) participants with HIV-1 RNA <50 copies/mL[25]

End point description:

The percentage of TN participants with HIV-1 RNA <50 copies/mL will be determined at the central laboratory with an Abbott Real Time PCR assay with a LLOD of 40 copies/mL. Participants who were TN at baseline and had data available are included.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[25] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Treatment Naive Cohort			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: percentage of participants				
number (confidence interval 95%)	100.0 (2.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cluster of differentiation 4+ (CD4+) T-cells in VS participants

End point title	Change from baseline in cluster of differentiation 4+ (CD4+) T-cells in VS participants[26]

End point description:

CD4+ T-cell counts were measured by a central laboratory. Negative and positive results represent a decrease and increase, respectively, from baseline CD4+ T-cell counts. All VS participants who received ≥1 dose of study intervention and had data available are included.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[26] - 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: A subset of participants is included in the PK assessment.

End point values	DOR/ISL: Virologically Suppressed Cohort			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: cells/mm^3				
arithmetic mean (confidence interval 95%)	-112.1 (-175.8 to -48.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of viral drug resistance to DOR

End point title	Incidence of viral drug resistance to DOR

End point description:

The number of participants with viral drug resistance to DOR was determined. Participants who received ≥1 dose of study intervention are included.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of viral drug resistance to ISL

End point title	Incidence of viral drug resistance to ISL

End point description:

The number of participants with viral drug resistance to ISL was determined. Participants who received ≥1 dose of study intervention are included.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of DOR/ISL tablet

End point title	Palatability of DOR/ISL tablet

End point description:

The palatability of the DOR/ISL tablet (whole or split) was assessed with a modified 5-point facial hedonic scale. Responses ranged from 1 ("very bad") to 5 ("very good"). Data show the number of VS and TN participants responding at each score at the designated time points. All VS and TN participants who received ≥1 dose of study intervention and have data available are included.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 4, and Week 24

End point values	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants				
Very Bad - Day 1	0	0		
Very Bad - Week 4	0	0		
Very Bad - Week 24	2	0		
Bad - Day 1	0	0		
Bad - Week 4	0	0		
Bad - Week 24	3	0		
Neither good or bad - Day 1	12	0		
Neither good or bad - Week 4	11	0		
Neither good or bad - Week 24	8	0		
Good - Day 1	9	2		
Good - Week 4	11	2		
Good - Week 24	5	1		
Very Good - Day 1	16	1		
Very Good - Week 4	15	1		
Very Good - Week 24	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability of DOR/ISL tablet

End point title	Acceptability of DOR/ISL tablet

End point description:

The acceptability of the DOR/ISL tablet (whole or split) was assessed. Acceptability was assessed by monitoring for refusing the tablet, throwing up or spitting out the tablet, and gagging on the tablet. Data show the number of VS and TN participants responding at each score at the designated time points. All VS and TN participants who received ≥1 dose of study intervention and have data available are included.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 4, and Week 24

End point values	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: participants				
Refusing - Day 1	0	0		
Refusing - Week 4	0	0		
Refusing - Week 24	0	0		
Throwing Up/Spitting Out - Day 1	0	0		
Throwing Up/Spitting Out - Week 4	0	0		
Throwing Up/Spitting Out - Week 24	0	0		
Gagging - Day 1	0	0		
Gagging - Week 4	0	0		
Gagging - Week 24	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored for up to ~15.3 months in the main study, and for an additional 12.5 months for those participating in the Extended Follow-Up period.

Adverse event reporting additional description:

All-cause mortality is assessed in all randomized participants. Adverse events (AEs) and serious AEs (SAEs) are assessed in all treated participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	DOR/ISL: Virologically Suppressed Cohort

Reporting group description:

VS participants (had taken stable 2- or 3-drug combination ART for ≥3 months) pediatric participants with HIV-1 infection receive DOR/ISL for 96 weeks.

Reporting group title	DOR/ISL: Treatment Naive Cohort: Extended Monitoring

Reporting group description:

A subset of TN participants who completed the study opted to participate in an extended safety monitoring period.

Reporting group title	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring

Reporting group description:

A subset of VS participants who completed the study opted to participate in an extended safety monitoring period.

Reporting group title	DOR/ISL: Treatment Naive Cohort

Reporting group description:

TN participants with HIV-1 infection receive DOR/ISL for 96 weeks.

Serious adverse events	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort: Extended Monitoring	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	0 / 1 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 1 (0.00%)	0 / 14 (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

Serious adverse events	DOR/ISL: Treatment Naive Cohort		

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DOR/ISL: Virologically Suppressed Cohort	DOR/ISL: Treatment Naive Cohort: Extended Monitoring	DOR/ISL: Virologically Suppressed Cohort: Extended Monitoring
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 37 (35.14%)	1 / 1 (100.00%)	12 / 14 (85.71%)
General disorders and administration site conditions			
Vaccination site pain			
subjects affected / exposed	3 / 37 (8.11%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Pyrexia			
subjects affected / exposed	3 / 37 (8.11%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Injection site pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			

Heavy menstrual bleeding			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 37 (8.11%)	0 / 1 (0.00%)	4 / 14 (28.57%)
occurrences (all)	4	0	7
Nasal congestion			
subjects affected / exposed	3 / 37 (8.11%)	0 / 1 (0.00%)	2 / 14 (14.29%)
occurrences (all)	3	0	4
Oropharyngeal pain			
subjects affected / exposed	4 / 37 (10.81%)	0 / 1 (0.00%)	3 / 14 (21.43%)
occurrences (all)	4	0	4
Rhinorrhoea			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	3 / 14 (21.43%)
occurrences (all)	2	0	4
Nasal mucosal disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
skin laceratio			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Headache			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Dry skin			

subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Dermatitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Nephropathy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 37 (8.11%)	0 / 1 (0.00%)	3 / 14 (21.43%)
occurrences (all)	3	0	4
Ear infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 37 (0.00%)	1 / 1 (100.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Post-acute COVID-19 syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Tonsillitis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Obesity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 1 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Non-serious adverse events	DOR/ISL: Treatment Naive Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)		
General disorders and administration site conditions			
Vaccination site pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Heavy menstrual bleeding			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nasal mucosal disorder			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Skin abrasion subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) skin laceratio subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Congenital, familial and genetic disorders Phimosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 0 / 3 (0.00%) 0		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) Dermatitis allergic subjects affected / exposed occurrences (all) Dry skin	1 / 3 (33.33%) 1 0 / 3 (0.00%) 0		

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nephropathy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Post-acute COVID-19 syndrome			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Tonsillitis			

subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Obesity subjects affected / exposed occurrences (all)	 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2020	AM01: the primary purposes of this amendment were to include a new cohort of ART-naïve participants; to remove the Week 12 visit and add visits at Weeks 8 and 16; to remove the 12-year-old lower age limit; to remove DOR PK assessments; and to extend the overall duration of the study to a total of 96 weeks.
12 March 2021	AM02: the primary purposes of this amendment were to include an assessment of the palatability of a split tablet, and to update inclusion criteria to include only participants who have no prior history of treatment failure.
08 February 2022	AM03: The primary purposes of the amendment were to discontinue dosing of study intervention in all participants based on Sponsor's acceptance of recommendations by the eDMC for pediatric HIV treatment trials, and to specify plans for detection and follow-up of participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 December 2021	Decreases in CD4+ T-cell and total lymphocyte counts were observed in some participants. Based on the totality of these changes noted across the ISL program occurring at doses of 0.75 mg and above, the pediatric external data monitoring committee (eDMC) recommended discontinuation of study intervention administration for all participants and to initiate safety monitoring.	-

Notes:

Limitations and caveats

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

Premature discontinuation of the study limits data interpretation of Week 48 endpoints.

Notes: