

**Clinical trial results:**

SMILE: Strategy for Maintenance of HIV suppression with once daily Integrase inhibitor +darunavir/ritonavir in childrEn (PENTA 17) - A two-arm, Phase 2/3 multicentre, open-label, randomised study evaluating safety and antiviral effect of current standard antiretroviral therapy compared to once daily integrase inhibitor administered with darunavir/ritonavir (DRV/r) in HIV-1 infected, virologically suppressed paediatric participants.

Summary

EudraCT number	2013-001476-37
Trial protocol	ES PT GB BE DE FR
Global end of trial date	17 November 2021

Results information

Result version number	v1 (current)
This version publication date	22 December 2021
First version publication date	22 December 2021

Trial information**Trial identification**

Sponsor protocol code	SMILE-PENTA17-ANRS152
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Additional study identifiers

ISRCTN number	ISRCTN11193709
ClinicalTrials.gov id (NCT number)	NCT02383108
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione Penta Onlus
Sponsor organisation address	Corso Stati Uniti 4, Padova, Italy, 35127
Public contact	Carlo Giaquinto (Sponsor; carlo.giaquinto@unipd.it); Alexandra Compagnucci (Clinical Project Leader), Inserm SC10-US19, 0033 145 59 52 90, alexandra.compagnucci@inserm.fr
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	20 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2020
Global end of trial reached?	Yes
Global end of trial date	17 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether children with chronic HIV infection on ART with suppressed viral load will maintain similar levels of suppression with once daily integrase inhibitor (INSTI) + darunavir/r compared to continued standard of care triple ART.

Protection of trial subjects:

Participant protection is evidenced by rigorous informed consent process and the protection of trial data. Participant information used age appropriate language so that participants and parents could make an informed decision. Only participants who were aware of their HIV status were approached for screening to avoid causing distress at disclosure of their status (if they did not know previously). The participant information sheet also explained that trial participants could be withdraw at any time during the trial without giving a reason, and that this would not affect the quality of the medical care they receive. Personal data was pseudonymised to ensure participant's identity is protected. Sites were trained to use an encrypted method to transfer data (i.e. using Galaxkey) and site staff were also trained on Good Clinical Practice. Only authorised study staff had access to trial information. Access to the trial database was restricted and only enabled following the appropriate training and completion of a non-disclosure of password form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2016
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	Portugal: 4
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	South Africa: 60
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Thailand: 47
Country: Number of subjects enrolled	Uganda: 110
Country: Number of subjects enrolled	Ukraine: 50

Worldwide total number of subjects	318
EEA total number of subjects	16

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)	4
Adolescents (12-17 years)	314
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	358 ^[1]
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Number of subjects completed	318
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failed ≥1 eligibility criteria: 33
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Reason: Number of subjects	Did not return <4wks of Screening: 1
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Reason: Number of subjects	Refusal: 4
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Reason: Number of subjects	Other: 2
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Notes:

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

Justification: 358 participants were screened, but 318 were randomised. Reasons for not randomising are documented here.

Period 1

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

Are arms mutually exclusive?	Yes
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Arm title	Intervention (Arm 1) - INSTI+DRV/r
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Arm description:

Arm 1. NRTI-sparing regimen: Once daily integrase inhibitor (INSTI) + darunavir/ritonavir (DRV/r)

Arm type	Experimental
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Investigational medicinal product name	Norvir
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Investigational medicinal product code	
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Other name	Ritonavir
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

Once daily 100 mg

Investigational medicinal product name	Prezista
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Investigational medicinal product code	
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Other name	Darunavir
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

Once daily 600 mg

Investigational medicinal product name	Prezista
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Investigational medicinal product code	
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Other name	Darunavir
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Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily 675 mg	
Investigational medicinal product name	Prezista
Investigational medicinal product code	
Other name	Darunavir
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily 800 mg	
Investigational medicinal product name	Vitekta
Investigational medicinal product code	
Other name	Elvitegravir
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily 85 mg	
Investigational medicinal product name	Vitekta
Investigational medicinal product code	
Other name	Elvitegravir
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily 150 mg	
Investigational medicinal product name	Tivicay
Investigational medicinal product code	
Other name	Dolutegravir
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Once daily 50 mg	
Arm title	Standard of care (Arm 2)
Arm description:	
Arm 2. Standard of care (continuing triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI)	
Arm type	Active comparator
Investigational medicinal product name	Comparator
Investigational medicinal product code	
Other name	Combination ART
Pharmaceutical forms	Tablet, Capsule, Syrup
Routes of administration	Oral use
Dosage and administration details:	
Combination ART	

Number of subjects in period 1	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)
Started	158	160
Completed	158	160

Baseline characteristics

Reporting groups

Reporting group title	Intervention (Arm 1) - INSTI+DRV/r
Reporting group description:	
Arm 1. NRTI-sparing regimen: Once daily integrase inhibitor (INSTI) + darunavir/ritonavir (DRV/r)	
Reporting group title	Standard of care (Arm 2)
Reporting group description:	
Arm 2. Standard of care (continuing triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI)	

Reporting group values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)	Total
Number of subjects	158	160	318
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)	2	2	4
Adolescents (12-17 years)	156	158	314
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	14.7	14.6	
inter-quartile range (Q1-Q3)	13.5 to 16.4	13.7 to 16.3	-
Gender categorical			
Units: Subjects			
Female	92	102	194
Male	66	58	124
Ethnic origin			
Units: Subjects			
White	32	38	70
Black-African	87	87	174
Black-other	0	1	1
Asian	29	22	51
Mixed black-white	2	1	3
Other	8	11	19
Route of HIV infection			
Units: Subjects			
Mother to child	146	155	301
Unknown	12	5	17
CDC stage			
Units: Subjects			
CDC N	40	39	79
CDC A	44	48	92

CDC B	45	50	95
CDC C	29	23	52
Weight-for-age z-score			
British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.			
Units: Subjects			
<-3	4	3	7
≥-3 to <-2	12	10	22
≥-2 to <0	90	96	186
≥0	52	51	103
Height-for-age z-score			
British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.			
Units: Subjects			
<-3	3	1	4
≥-3 to <-2	16	14	30
≥-2 to <0	103	99	202
≥0	36	46	82
BMI-for-age z-score			
British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.			
Units: Subjects			
<-3	1	1	2
≥-3 to <-2	3	2	5
≥-2 to <0	77	85	162
≥0	77	72	149
HIV-1 RNA			
To meet the criteria for enrolment, all HIV-1 RNA had to be <50 cp/ml at the screening visit. At the randomisation visit, HIV-1 RNA may be ≥50 cp/ml.			
Units: Subjects			
HIV-1 RNA<50	154	155	309
HIV-1 RNA≥50	3	5	8
Not recorded	1	0	1
Menarche in females			
Units: Subjects			
No	12	22	34
Yes	80	80	160
NA - Males	66	58	124
Tanner scores: Pubic hair			
Note: SOC arm: 159/160 had a pubic hair measured. Tanner scores should only be measured in children ≥8 years for age but one participant was 7.6 years at baseline. So, this child was classified as "Set to missing", hence not included in the analysis.			
Units: Subjects			
Score 1	9	3	12
Score 2	25	22	47
Score 3	47	61	108
Score 4	50	51	101
Score 5	27	21	48
Not recorded	0	1	1
Set to missing	0	1	1
Tanner scores: Female breasts			
Tanner scores should only be measured in children ≥8 years for age but one participant in SOC arm was 7.6 years at baseline. So, this child was classified as "Set to missing", hence not included in the analysis.			

Units: Subjects			
Score 1	4	0	4
Score 2	9	11	20
Score 3	25	39	64
Score 4	34	37	71
Score 5	20	14	34
NA - Male	66	58	124
Set to missing	0	1	1
Tanner scores: Male genitalia			
Units: Subjects			
Score 1	2	1	3
Score 2	13	7	20
Score 3	25	21	46
Score 4	16	21	37
Score 5	10	7	17
Not recorded	0	1	1
NA - Female	92	102	194
Number of different drugs ever received pre-randomisation			
Count excludes drugs used for PMTCT as well as booster drugs given as a single entity (Ritonavir and Cobicistat).			
Units: Subjects			
Three	48	56	104
Four	49	39	88
Five	27	30	57
≥Six	34	35	69
Number of different NRTIs ever received pre-randomisation			
NRTI: Nucleoside Reverse Transcriptase Inhibitor			
Units: Subjects			
Two	54	68	122
Three	63	43	106
≥Four	41	49	90
Number of different NNRTIs ever received pre-randomisation			
NNRTI: Non-nucleoside reverse-transcriptase inhibitors			
Units: Subjects			
Zero	45	37	82
One	95	112	207
Two	18	11	29
Number of different PIs ever received pre-randomisation			
PI: Protease Inhibitor			
Units: Subjects			
Zero	86	87	173
One	50	52	102
Two	20	18	38
Three	2	3	5
Number of different INSTIs ever received pre-randomisation			
INSTI: integrase strand transfer inhibitors. Note: One participant had previous exposure to INSTI for 12 days (<2weeks which meets inclusion criteria)			
Units: Subjects			
Zero	158	159	317

One	0	1	1
Number of participants exposed to:			
NNRTI: Non-nucleoside reverse-transcriptase inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; INSTI: integrase strand transfer inhibitors.			
Units: Subjects			
NRTI+PI only	45	37	82
NRTI+NNRTI only	86	87	173
NRTI+NNRTI+PI only	27	35	62
NRTI+NNRTI+PI+INSTI	0	1	1
Baseline regimen same as ART initiation regimen			
Units: Subjects			
No	102	97	199
Yes	56	63	119
Weight			
Units: Kg			
median	47.3	48.0	
inter-quartile range (Q1-Q3)	42.9 to 51.8	44.0 to 53.0	-
Height			
Units: cm			
median	157.4	157.6	
inter-quartile range (Q1-Q3)	152.0 to 162.3	152.8 to 163.3	-
Body mass index			
Units: kg/m2			
median	19.1	19.2	
inter-quartile range (Q1-Q3)	17.7 to 21.1	17.9 to 21.1	-
CD4%			
Units: Percentage			
median	36	36	
inter-quartile range (Q1-Q3)	32 to 40	32 to 41	-
CD4			
Units: cells/mm3			
median	775	803	
inter-quartile range (Q1-Q3)	636 to 967	630 to 985	-
CD8%			
CD8 tests are optional, according to feasibility at the sites.			
Units: Percent			
median	30	29	
inter-quartile range (Q1-Q3)	25 to 34	25 to 35	-
CD8			
CD8 tests are optional, according to feasibility at the sites.			
Units: cells/mm3			
median	627	680	
inter-quartile range (Q1-Q3)	513 to 847	544 to 837	-
CD4%/CD8% ratio			
CD8 tests are optional, according to feasibility at the sites.			
Units: Ratio			
median	1.2	1.2	
inter-quartile range (Q1-Q3)	0.9 to 1.5	1.0 to 1.7	-
Total Lymphocytes			
Total lymphocytes tests are optional, according to feasibility at the sites.			
Units: cells/mm3			

median	2171	2181	
inter-quartile range (Q1-Q3)	1895 to 2630	1856 to 2661	-
Cumulative ART exposure to all classes			
Count excludes booster drugs given as a single entity (Ritonavir and Cobicistat)			
Units: Years			
median	11	11	
full range (min-max)	1 to 16	2 to 17	-
Cumulative exposure to NRTIs			
NRTI: Nucleoside Reverse Transcriptase Inhibitor			
Units: Years			
median	11	11	
full range (min-max)	1 to 16	2 to 17	-
Cumulative exposure to NNRTIs			
NNRTI: Non-nucleoside reverse-transcriptase inhibitors			
Units: Years			
median	5	5	
full range (min-max)	0 to 15	0 to 17	-
Cumulative exposure to PIs			
PI: Protease Inhibitor			
Units: Years			
median	0	0	
full range (min-max)	0 to 16	0 to 15	-

End points

End points reporting groups

Reporting group title	Intervention (Arm 1) - INSTI+DRV/r
Reporting group description:	
Arm 1. NRTI-sparing regimen: Once daily integrase inhibitor (INSTI) + darunavir/ritonavir (DRV/r)	
Reporting group title	Standard of care (Arm 2)
Reporting group description:	
Arm 2. Standard of care (continuing triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI)	

Primary: Virological failure: Confirmed HIV-1 RNA ≥ 50 c/ml by 48 weeks

End point title	Virological failure: Confirmed HIV-1 RNA ≥ 50 c/ml by 48 weeks
End point description:	
Confirmed HIV-1 RNA ≥ 50 c/mL at any time up to week 48 (end of window is 54 weeks)	
End point type	Primary
End point timeframe:	
Any time from randomisation to 48(+6) weeks after randomisation.	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
Reached endpoint	8	12		
Did not reach endpoint	150	148		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Difference in estimated probability of failure (INSTI+DRV/r - SOC) by 48 weeks, adjusted for stratification factors (adjusted Kaplan-Meier estimates)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.025

Notes:

[1] - Non-inferiority margin is 10%. Non-inferiority will be inferred if the upper bound of the two-sided bias corrected 95% CI for the difference between the two groups (INSTI+DRV/r – SOC) is less than 10%. Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Statistical analysis title	Sensitivity analysis
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Statistical analysis description:

Difference in the estimated probability of failure (INSTI+DRV/r - SOC) by 48 weeks, unadjusted for stratification factors (unadjusted Kaplan-Meier estimates)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Mean difference (final values)
Point estimate	-0.025

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.081
upper limit	0.032

Notes:

[2] - Non-inferiority margin is 10%. Non-inferiority will be inferred if the upper bound of the two-sided bias corrected 95% CI for the difference between the two groups (INSTI+DRV/r – SOC) is less than 10%. Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Statistical analysis title	Per-Protocol analysis (adjusted)
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Statistical analysis description:

Difference in estimated probability of failure (INSTI+DRV/r - SOC) by 48 weeks, adjusted for stratification factors (adjusted Kaplan-Meier estimates). Per protocol analysis of the primary endpoint was performed by censoring the follow-up of all children who discontinued any component of the allocated treatment for any reason, except for change due to change in national clinical guidelines in the SOC arm. Treatment interruption for >31 days for any reason is defined as treatment discontinuation.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Mean difference (final values)
Point estimate	-0.026

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.077
upper limit	0.022

Notes:

[3] - Non-inferiority margin is 10%. Non-inferiority will be inferred if the upper bound of the two-sided bias corrected 95% CI for the difference between the two groups (INSTI+DRV/r – SOC) is less than 10%. Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Statistical analysis title	Per-Protocol analysis (unadjusted)
Statistical analysis description:	
Difference in estimated probability of failure (INSTI+DRV/r - SOC) by 48 weeks, unadjusted for stratification factors (unadjusted Kaplan-Meier estimates). Per protocol analysis of the primary endpoint was performed by censoring the follow-up of all children who discontinued any component of the allocated treatment for any reason, except for change in national clinical guidelines in the SOC arm. Treatment interruption for >31 days for any reason is defined as treatment discontinuation.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Mean difference (final values)
Point estimate	-0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.027

Notes:

[4] - Non-inferiority margin is 10%. Non-inferiority will be inferred if the upper bound of the two-sided bias corrected 95% CI for the difference between the two groups (INSTI+DRV/r – SOC) is less than 10%. Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Statistical analysis title	Time to virological failure (adjusted)
Statistical analysis description:	
Cox regression analysis examining time to confirmed HIV-1 RNA ≥ 50 c/ml by 48 weeks, adjusted for stratification factors	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.356
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.61

Statistical analysis title	Time to virological failure (unadjusted)
Statistical analysis description:	
Cox regression analysis examining time to confirmed HIV-1 RNA ≥ 50 c/ml by 48 weeks, unadjusted for stratification factors	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

	2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.366
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.62

Secondary: HIV-1 RNA ≥ 50 c/ml at week 24

End point title	HIV-1 RNA ≥ 50 c/ml at week 24
End point description:	
Comparison of proportion of participants with HIV-1 RNA ≥ 50 c/ml at week 24 [cross sectional comparison]	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
HIV-1 RNA <50	151	153		
HIV-1 RNA ≥ 50	7	7		

Statistical analyses

Statistical analysis title	Difference in proportion with HIV-1 RNA ≥ 50 (unadj)
Statistical analysis description:	
Difference in proportion of participants with HIV-1 RNA ≥ 50 c/ml at week 24 (Chi-squared test). HIV-1 RNA result nearest to scheduled visit week 24 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.981
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.046

Statistical analysis title	Difference in proportion with HIV-1 RNA \geq 50 (adj)
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Statistical analysis description:

Difference in proportion of participants with HIV-1 RNA \geq 50c/ml at week 24 (Logistic regression p-value adjusted for stratification factors). HIV-1 RNA result nearest to scheduled visit week 24 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.985
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.046

Secondary: HIV-1 RNA \geq 50c/ml at week 48

End point title	HIV-1 RNA \geq 50c/ml at week 48
End point description:	
Comparison of proportion of participants with HIV-1 RNA \geq 50c/ml at week 48 [cross sectional comparison]	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150 ^[5]	156 ^[6]		
Units: People				
HIV-1 RNA <50	143	143		
HIV-1 RNA ≥50	7	13		

Notes:

[5] - Participants with a measurement at week 48

[6] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in proportion with HIV-1 RNA≥50 (unadj)
Statistical analysis description:	
Difference in proportion of participants with HIV-1 RNA ≥50c/ml at week 48 (Chi-squared test). HIV-1 RNA result nearest to scheduled visit week 48 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.195
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.018

Statistical analysis title	Difference in proportion with HIV-1 RNA≥50 (adj)
Statistical analysis description:	
Difference in proportion of participants with HIV-1 RNA ≥50c/ml at week 48 (Logistic regression p-value adjusted for stratification factors). HIV-1 RNA result nearest to scheduled visit week 48 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.195
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.037

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.018

Secondary: HIV-1 RNA ≥50c/ml at week 48 (FDA snapshot)

End point title	HIV-1 RNA ≥50c/ml at week 48 (FDA snapshot)
End point description:	
Comparison of proportion of participants with HIV-1 RNA ≥50c/ml at week 48 [FDA SNAPSHOT ALGORITHM]	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
HIV-1 RNA ≥50 at week 48	7	7		
HIV-1 RNA <50c/mL at week 48	139	147		
No virologic data in week 48 window	12	6		

Statistical analyses

Statistical analysis title	Difference in proportion with HIV-1 RNA≥50
Statistical analysis description:	
Difference in proportion (95% CI) at week 48 estimated by Mantel-Haenszel weighted mean of proportions in each stratum. P-value derived from Mantel-Haenszel Chi-squared test.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
P-value	= 0.985
Method	Mantel-Haenszel Chi-squared test
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	4.69

Notes:

[7] - Non-inferiority margin is 10%. Non-inferiority will be inferred if the upper bound of the two-sided bias corrected 95% CI for the difference between the two groups (INSTI+DRV/r – SOC) is less than 10%. Point estimate and 95% CI are presented as percentages.

Secondary: HIV-1 RNA ≥ 400 c/ml at week 24

End point title	HIV-1 RNA ≥ 400 c/ml at week 24
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End point description:

Comparison of proportion of participants with HIV-1 RNA ≥ 400 c/ml at week 24 [cross sectional comparison]

End point type	Secondary
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End point timeframe:

Week 24

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
HIV-1 RNA <400	156	156		
HIV-1 RNA ≥ 400	2	4		

Statistical analyses

Statistical analysis title	Difference in proportion with HIV1 RNA ≥ 400 (unadj)
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Statistical analysis description:

Difference in proportion of participants with HIV-1 RNA ≥ 400 c/ml at week 24 (Chi-squared test). HIV-1 RNA result nearest to scheduled visit week 24 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
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Number of subjects included in analysis	318
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.419
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Method	Chi-squared
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Parameter estimate	Mean difference (final values)
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Point estimate	-0.012
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-0.042
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upper limit	0.017
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Statistical analysis title	Difference in proportion with HIV1 RNA ≥ 400 (adj)
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Statistical analysis description:

Difference in proportion of participants with HIV-1 RNA ≥ 400 c/ml at week 24 (Logistic regression p-value adjusted for stratification factors). HIV-1 RNA result nearest to scheduled visit week 24 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.428
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.017

Secondary: HIV-1 RNA ≥ 400 c/ml at week 48

End point title	HIV-1 RNA ≥ 400 c/ml at week 48
End point description:	
Comparison of proportion of participants with HIV-1 RNA ≥ 400 c/ml at week 48 [cross sectional comparison]	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150 ^[8]	156 ^[9]		
Units: People				
HIV-1 RNA <400	146	149		
HIV-1 RNA ≥ 400	4	7		

Notes:

[8] - Participants with a measurement at week 48

[9] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in proportion with HIV1 RNA ≥ 400 (unadj)
Statistical analysis description:	
Difference in proportion of participants with HIV-1 RNA ≥ 400 c/ml at week 48 (Chi-squared test). HIV-1 RNA result nearest to scheduled visit week 48 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm

	2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.392
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.023

Statistical analysis title	Difference in proportion with HIV1 RNA \geq 400 (adj)
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Statistical analysis description:

Difference in proportion of participants with HIV-1 RNA \geq 400c/ml at week 48 (Logistic regression p-value adjusted for stratification factors). HIV-1 RNA result nearest to scheduled visit week 48 is used when multiple results fall in the same nominal week window (as described in SAP). Point estimate and 95% CI are not presented as percentages; for percentages, values need to be multiplied by 100.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.392
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.023

Secondary: New or recurrent CDC stage C or severe stage B* event or death

End point title	New or recurrent CDC stage C or severe stage B* event or death
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End point description:

Severe CDC stage B is defined as severe lung disease including LIP, nephropathy, cardiomyopathy, failure to thrive in absence of remediable causes, recurrent bacterial pneumonia, severe or recurrent oral candidiasis.

End point type	Secondary
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End point timeframe:

Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[10]	160		
Units: People				
New CDC stage C event	0	0		
New severe CDC stage B event	1	0		
Death	0	0		

Notes:

[10] - Severe CDC stage B event [Nephropathy; Grade 3]

Statistical analyses

Statistical analysis title	Participants with new CDC stage C/severe stage B
Statistical analysis description:	
Fisher's exact test used to compare number of participants with ≥ 1 new CDC stage C or severe stage B events between arms.	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.497
Method	Fisher exact

Secondary: New resistance mutations

End point title	New resistance mutations
End point description:	
Comparison of proportion of participants with resistance mutations. Resistance defined according to IAS 2019.	
Stored samples (one per participant) were selected for resistance testing in those who have met the primary endpoint (confirmed VL \geq 50cp/ml) up to week 48 censoring date. The primary aim of selection was to select the latest sample with VL available over limit of detection at site at/after failure and before any treatment change (unless treatment change was prior to first of 2 consecutive VL \geq 50cp/ml) by week 48 censoring date.	
End point type	Secondary
End point timeframe:	
Any time from randomisation to 48(+6) weeks after randomisation.	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[11]	5 ^[12]		
Units: People				
Major IAS mutation	1	2		
No major IAS mutation	5	3		

Notes:

[11] - Participants meeting primary endpoint by week 48 with resistance test available

[12] - Participants meeting primary endpoint by week 48 with resistance test available

Statistical analyses

Statistical analysis title	Proportions with major resistance (unadjusted)
Statistical analysis description:	
Comparison of proportions with major resistance (%) of those meeting primary endpoint by week 48 and with a test available (Chi-squared test). Point estimate and 95% CI are presented as percentages.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.387
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-23.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.61
upper limit	28.95

Statistical analysis title	Proportions with major resistance (adjusted)
Statistical analysis description:	
Comparison of proportions with major resistance (%) of those meeting primary endpoint by week 48 and with a test available (Logistic regression p-value adjusted for stratification factors). Point estimate and 95% CI are presented as percentages.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.711
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-23.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.61
upper limit	28.95

Secondary: Mean change in CD4% from randomisation to week 24

End point title	Mean change in CD4% from randomisation to week 24
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End point description:

Reporting mean change from the global baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 24 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	158 ^[13]		
Units: Percentage				
arithmetic mean (standard error)	-1.6 (± 0.3)	-0.1 (± 0.3)		

Notes:

[13] - Participants with a measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
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Statistical analysis description:

Linear regression of CD4% at week 24, adjusting for baseline CD4% and stratification factors.

Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.6

Secondary: Mean change in CD4% from randomisation to week 48

End point title	Mean change in CD4% from randomisation to week 48
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End point description:

Reporting mean change from the global baseline value (across both arms).

End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150 ^[14]	156 ^[15]		
Units: Percentage				
arithmetic mean (standard error)	-1.8 (± 0.4)	0.2 (± 0.4)		

Notes:

[14] - Participants with a measurement at week 48

[15] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of CD4% at week 48, adjusting for baseline CD4% and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-0.9

Secondary: Mean change in CD4 count from randomisation to week 24

End point title	Mean change in CD4 count from randomisation to week 24
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	158 ^[16]		
Units: cells/mm ³				
arithmetic mean (standard error)	-31.2 (± 16.3)	0.1 (± 16.3)		

Notes:

[16] - Participants with a measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description:	
Linear regression of CD4 count at week 24, adjusting for baseline CD4 count and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-31.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76.5
upper limit	13.5

Secondary: Mean change in CD4 count from randomisation to week 48

End point title	Mean change in CD4 count from randomisation to week 48
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150 ^[17]	156 ^[18]		
Units: cells/mm ³				
arithmetic mean (standard error)	-43.8 (± 16.5)	5.2 (± 16.1)		

Notes:

[17] - Participants with a measurement at week 48

[18] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of CD4 count at week 48, adjusting for baseline CD4 count and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-48.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93.4
upper limit	-3.2

Secondary: Changes in ART regimen

End point title	Changes in ART regimen
End point description:	
ART changes that do not involve switch of any of the ART components to a different one are not included: change for "body size change/recalculation", "regimen changes to mornings", "switch to FDC containing the same ART components", "switch from trial DRV to non-trial DRV". ART change is defined as any change after randomisation day.	
End point type	Secondary
End point timeframe:	
Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
On initial regimen at end of trial	145	131		
Not on initial regimen at end of trial	13	29		

Statistical analyses

Statistical analysis title	Time to first ART change (adjusted)
Statistical analysis description:	
End of trial is defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date). With the exception of changes for change in national clinical guidelines, any other ART changes for any reason are included in the analysis. Regimen interruptions for >31 days are considered as ART discontinuations and are also included in the analysis. Cox regression model examining time to first ART change, adjusted for stratification factors.	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.777
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.38

Statistical analysis title	Time to first ART change (unadjusted)
Statistical analysis description:	
End of trial is defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date). With the exception of changes for change in national clinical guidelines, any other ART changes for any reason are included in the analysis. Regimen interruptions for >31 days are considered as ART discontinuations and are also included in the analysis. Cox regression model examining time to first ART change (unadjusted).	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.82
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.33

Secondary: Mean change in fasting total cholesterol from randomisation to week 24

End point title	Mean change in fasting total cholesterol from randomisation to week 24
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End point description:

Reporting mean change from the global fasting baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 24 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[19]	141 ^[20]		
Units: mg/dL				
arithmetic mean (standard error)	4.3 (± 2.0)	-2.2 (± 2.0)		

Notes:

[19] - Participants with a fasting measurement at week 24

[20] - Participants with a fasting measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
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Statistical analysis description:

Linear regression of fasting total cholesterol at week 24, adjusting for baseline total cholesterol and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)

Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	11.9

Secondary: Mean change in fasting total cholesterol from randomisation to week 48

End point title	Mean change in fasting total cholesterol from randomisation to week 48
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End point description:	
Reporting mean change from the global fasting baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136 ^[21]	143 ^[22]		
Units: mg/dL				
arithmetic mean (standard error)	-0.6 (± 2.2)	-1.0 (± 2.2)		

Notes:

[21] - Participants with a fasting measurement at week 48

[22] - Participants with a fasting measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of fasting total cholesterol at week 48, adjusting for baseline total cholesterol and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.916
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	6.4

Secondary: Mean change in fasting triglycerides from randomisation to week 24

End point title	Mean change in fasting triglycerides from randomisation to week 24
End point description:	
Reporting mean change from the global fasting baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[23]	141 ^[24]		
Units: mg/dL				
arithmetic mean (standard error)	1.5 (± 4.4)	-0.7 (± 4.4)		

Notes:

[23] - Participants with a fasting measurement at week 24

[24] - Participants with a fasting measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
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Statistical analysis description:

Linear regression of fasting triglycerides at week 24, adjusting for baseline triglycerides and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.697
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	14.6

Secondary: Mean change in fasting triglycerides from randomisation to week 48

End point title	Mean change in fasting triglycerides from randomisation to week 48
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End point description:

Reporting mean change from the global fasting baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136 ^[25]	143 ^[26]		
Units: mg/dL				
arithmetic mean (standard error)	3.3 (± 5.6)	5.6 (± 5.4)		

Notes:

[25] - Participants with a fasting measurement at week 48

[26] - Participants with a fasting measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of fasting triglycerides at week 48, adjusting for baseline triglycerides and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.774
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3
upper limit	12.9

Secondary: Mean change in fasting LDL from randomisation to week 24

End point title	Mean change in fasting LDL from randomisation to week 24
End point description:	
Reporting mean change from the global fasting baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[27]	141 ^[28]		
Units: mg/dL				
arithmetic mean (standard error)	9.0 (± 1.7)	-1.0 (± 1.7)		

Notes:

[27] - Participants with a fasting measurement at week 24

[28] - Participants with a fasting measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of fasting LDL at week 24, adjusting for baseline LDL and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	14.6

Secondary: Mean change in fasting LDL from randomisation to week 48

End point title	Mean change in fasting LDL from randomisation to week 48
End point description: Reporting mean change from the global fasting baseline value (across both arms).	
End point type	Secondary
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136 ^[29]	141 ^[30]		
Units: mg/dL				
arithmetic mean (standard error)	2.8 (± 1.9)	-2.1 (± 1.9)		

Notes:

[29] - Participants with a fasting measurement at week 48

[30] - Participants with a fasting measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of fasting LDL at week 48, adjusting for baseline LDL and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.088
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	10

Secondary: Mean change in fasting HDL from randomisation to week 24

End point title	Mean change in fasting HDL from randomisation to week 24
End point description: Reporting mean change from the global fasting baseline value (across both arms).	
End point type	Secondary
End point timeframe: Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[31]	141 ^[32]		
Units: mg/dL				
arithmetic mean (standard error)	-5.6 (± 0.9)	-1.8 (± 0.9)		

Notes:

[31] - Participants with a fasting measurement at week 24

[32] - Participants with a fasting measurement at week 24

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of fasting HDL at week 24, adjusting for baseline HDL and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r

Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-1.5

Secondary: Mean change in fasting HDL from randomisation to week 48

End point title	Mean change in fasting HDL from randomisation to week 48
End point description:	Reporting mean change from the global fasting baseline value (across both arms).
End point type	Secondary
End point timeframe:	Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136 ^[33]	141 ^[34]		
Units: mg/dL				
arithmetic mean (standard error)	-6.4 (± 1.0)	-2.4 (± 0.9)		

Notes:

[33] - Participants with a fasting measurement at week 48

[34] - Participants with a fasting measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	Linear regression of fasting HDL at week 48, adjusting for baseline HDL and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	-1.4

Secondary: Mean change in weight from randomisation to week 24

End point title	Mean change in weight from randomisation to week 24
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe: Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: Kg				
arithmetic mean (standard error)	3.07 (± 0.2)	1.79 (± 0.2)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of weight at week 24, adjusting for baseline weight and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.9

Secondary: Mean change in weight from randomisation to week 48

End point title	Mean change in weight from randomisation to week 48
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End point description:

Reporting mean change from the global baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146 ^[35]	155 ^[36]		
Units: Kg				
arithmetic mean (standard error)	5.08 (± 0.3)	3.11 (± 0.3)		

Notes:

[35] - Participants with a measurement at week 48

[36] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
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Statistical analysis description:

Linear regression of weight at week 48, adjusting for baseline weight and stratification factors.

Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.9

Secondary: Mean change in weight-for-age z-score from randomisation to week 24

End point title	Mean change in weight-for-age z-score from randomisation to week 24
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End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: z-score				
arithmetic mean (standard error)	0.15 (± 0.0)	0.01 (± 0.0)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
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Statistical analysis description:

Linear regression of weight-for-age z-score at week 24, adjusting for baseline weight-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.2

Secondary: Mean change in weight-for-age z-score from randomisation to week 48

End point title	Mean change in weight-for-age z-score from randomisation to week 48
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End point description:

Reporting mean change from the global baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146 ^[37]	155 ^[38]		
Units: z-score				
arithmetic mean (standard error)	0.19 (± 0.0)	-0.02 (± 0.0)		

Notes:

[37] - Participants with a measurement at week 48

[38] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
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Statistical analysis description:

Linear regression of weight-for-age z-score at week 48, adjusting for baseline weight-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.3

Secondary: Mean change in height from randomisation to week 24

End point title	Mean change in height from randomisation to week 24
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End point description:

Reporting mean change from the global baseline value (across both arms).

End point type	Secondary
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End point timeframe:

Randomisation and week 24 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: cm				
arithmetic mean (standard error)	1.64 (\pm 0.1)	1.55 (\pm 0.1)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description:	
Linear regression of height at week 24, adjusting for baseline height and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.641
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.4

Secondary: Mean change in height from randomisation to week 48

End point title	Mean change in height from randomisation to week 48
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145 ^[39]	153 ^[40]		
Units: cm				
arithmetic mean (standard error)	3.10 (\pm 0.2)	2.76 (\pm 0.2)		

Notes:

[39] - Participants with a measurement at week 48

[40] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of height at week 48, adjusting for baseline height and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9

Secondary: Mean change in height-for-age z-score from randomisation to week 24

End point title	Mean change in height-for-age z-score from randomisation to week 24
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe: Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: z-score				
arithmetic mean (standard error)	0.00 (± 0.0)	0.01 (± 0.0)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description:	
Linear regression of height-for-age z-score at week 24, adjusting for baseline height-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.847
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Mean change in height-for-age z-score from randomisation to week 48

End point title	Mean change in height-for-age z-score from randomisation to week 48
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145 ^[41]	153 ^[42]		
Units: z-score				
arithmetic mean (standard error)	0.01 (± 0.0)	-0.00 (± 0.0)		

Notes:

[41] - Participants with a measurement at week 48

[42] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of height-for-age z-score at week 48, adjusting for baseline height-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-	

scores. This reference data covers the full age range (0–23 years) of SMILE participants.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.754
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Secondary: Onset of menarche at week 48

End point title	Onset of menarche at week 48
End point description:	
Comparison of proportion of female participants reaching menarche at week 48	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12 ^[43]	22 ^[44]		
Units: People				
No (not reached menarche at week 48)	4	4		
Yes (reached menarche at week 48))	8	18		

Notes:

[43] - Number of female participants who had not already reached menarche at baseline.

[44] - Number of female participants who had not already reached menarche at baseline.

Statistical analyses

Statistical analysis title	Difference in proportion reaching menarche at w48
Statistical analysis description:	
Difference in proportion of female participants reaching menarche at week 48 (Logistic regression p-value adjusted for stratification factors)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.332
Method	Regression, Logistic

Secondary: Changes in tanner scores (pubic hair) by week 48

End point title	Changes in tanner scores (pubic hair) by week 48
End point description:	
Reporting proportion changes in ordered categorical variable (Tanner Score - pubic hair) from baseline, week 24 and 48	
End point type	Secondary
End point timeframe:	
Randomisation, week 24 and week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143 ^[45]	153 ^[46]		
Units: People	143	153		

Notes:

[45] - Participants with a measurement at week 48

[46] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Changes in pubic hair tanner scores by week 48
Statistical analysis description:	
Ordered logistic mixed model comparing ordered outcome across treatment arms over time up to week 48 with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline Tanner scores, age at randomisation and Region; assuming proportional odds.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	Ordered logistic mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.32

Secondary: Changes in tanner scores (female breast) by week 48

End point title	Changes in tanner scores (female breast) by week 48
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End point description:

Reporting proportion changes in ordered categorical variable (Tanner Score - female breast) from baseline, week 24 and 48

End point type	Secondary
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End point timeframe:

Randomisation, week 24 and week 48

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86 ^[47]	101 ^[48]		
Units: People	86	101		

Notes:

[47] - Female participants with a measurement at week 48, out of 92 females enrolled in arm 1.

[48] - Female participants with a measurement at week 48, out of 102 females enrolled in arm 2.

Statistical analyses

Statistical analysis title	Changes in female breast tanner scores by week 48
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Statistical analysis description:

Ordered logistic mixed model was fitted to compare ordered outcome across treatment arms over time up to week 48 with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline Tanner scores and strata]; assuming proportional odds.

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.097
Method	Ordered logistic mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.66

Secondary: Changes in tanner scores (male genital) by week 48

End point title	Changes in tanner scores (male genital) by week 48
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End point description:

Reporting proportion changes in ordered categorical variable (Tanner Score - male genital) from baseline, week 24 and 48

End point type	Secondary
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End point timeframe:

Randomisation, week 24 and week 48

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58 ^[49]	52 ^[50]		
Units: People	58	52		

Notes:

[49] - Male participants with a measurement at week 48, out of 66 males enrolled in arm 1.

[50] - Male participants with a measurement at week 48, out of 58 males enrolled in arm 2.

Statistical analyses

Statistical analysis title	Changes in male genital scores by week 48
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Statistical analysis description:

Ordered logistic mixed model was fitted to compare ordered outcome across treatment arms over time up to week 48 with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline Tanner scores and strata]; assuming proportional odds.

Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	Ordered logistic mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	6.84

Secondary: Adherence (participant response): Missed a dose over the last 3 days

End point title	Adherence (participant response): Missed a dose over the last 3 days
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End point description:

Participants were asked if they missed a dose over the last 3 days

End point type	Secondary
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End point timeframe:

Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[51]	160 ^[52]		
Units: People				
Missed a dose over the last 3 days: week 4	6	6		
Missed a dose over the last 3 days: week 12	6	5		
Missed a dose over the last 3 days: week 24	6	7		
Missed a dose over the last 3 days: week 36	6	9		
Missed a dose over the last 3 days: week 48	7	5		

Notes:

[51] - Denominator differed by study week: Week 4=157; Week 12=158; Week 24=158; Week 36=155; Week 48=151

[52] - Denominator differed by study week: Week 4=159; Week 12=159; Week 24=157; Week 36=155; Week 48=156

Statistical analyses

Statistical analysis title	Proportions missed a dose over the last 3 days
Statistical analysis description:	
Logistic mixed model was fitted to compare binary outcome across treatment arms over time with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answer and strata].	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.342
Method	Logistic mixed model

Secondary: Adherence (participant response): Missed any dose since last clinic visit

End point title	Adherence (participant response): Missed any dose since last clinic visit
End point description:	
Participants were asked if they missed any dose since last clinic visit	
End point type	Secondary
End point timeframe:	
Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[53]	160 ^[54]		
Units: People				
Missed any dose since last clinic visit: Week 4	15	18		
Missed any dose since last clinic visit: Week 12	23	17		
Missed any dose since last clinic visit: Week 24	32	28		
Missed any dose since last clinic visit: Week 36	26	23		
Missed any dose since last clinic visit: Week 48	24	17		

Notes:

[53] - Denominator differed by study week: Week 4=157; Week 12=158; Week 24=158; Week 36=155; Week 48=151

[54] - Denominator differed by study week: Week 4=159; Week 12=159; Week 24=157; Week 36=155; Week 48=156

Statistical analyses

Statistical analysis title	Proportions missed any dose since last visit
Statistical analysis description:	
Logistic mixed model was fitted to compare binary outcome across treatment arms over time with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answer and strata].	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.32
Method	Logistic mixed model

Secondary: Adherence (participant response): Adherence rating since the last clinic visit

End point title	Adherence (participant response): Adherence rating since the last clinic visit
End point description:	
Participants were asked to complete adherence rating since the last clinic visit	
End point type	Secondary
End point timeframe:	
Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[55]	160 ^[56]		
Units: People				
Week 4: Excellent	81	73		
Week 4: Very Good	61	70		
Week 4: Fair	10	6		
Week 4: Not that good	0	3		
Week 4: Not recorded	5	7		
Week 12: Excellent	83	69		
Week 12: Very Good	54	75		
Week 12: Fair	15	9		
Week 12: Not that good	1	1		
Week 12: Not recorded	5	5		
Week 24: Excellent	74	65		
Week 24: Very Good	64	77		
Week 24: Fair	10	10		
Week 24: Not that good	2	1		
Week 24: Not recorded	8	4		
Week 36: Excellent	74	79		
Week 36: Very Good	66	59		
Week 36: Fair	11	9		
Week 36: Not that good	0	3		
Week 36: Not recorded	4	5		
Week 48: Excellent	63	62		
Week 48: Very Good	76	80		
Week 48: Fair	7	7		
Week 48: Not that good	1	1		
Week 48: Not recorded	4	6		

Notes:

[55] - Denominator differed by study week: Week 4=157; Week 12=158; Week 24=158; Week 36=155; Week 48=151

[56] - Denominator differed by study week: Week 4=159; Week 12=159; Week 24=157; Week 36=155; Week 48=156

Statistical analyses

Statistical analysis title	Comparing adherence rating since the last visit
Statistical analysis description:	
Ordered logistic mixed model was fitted to compare ordered outcome across treatment arms with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answers and strata].	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.423
Method	Ordered logistic mixed model

Secondary: Adherence (parent response): Missed a dose over the last 3 days

End point title	Adherence (parent response): Missed a dose over the last 3 days
End point description: Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.	
End point type	Secondary
End point timeframe: Parents/carers were asked if their child has missed a dose over the last 3 days	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[57]	160 ^[58]		
Units: People				
Missed a dose over the last 3 days: week 4	2	6		
Missed a dose over the last 3 days: week 12	4	4		
Missed a dose over the last 3 days: week 24	4	2		
Missed a dose over the last 3 days: week 36	5	6		
Missed a dose over the last 3 days: week 48	4	4		

Notes:

[57] - Denominator differed by study week: Week 4=143; Week 12=138; Week 24=137; Week 36=130; Week 48=124

[58] - Denominator differed by study week: Week 4=147; Week 12=143; Week 24=134; Week 36=134; Week 48=138

Statistical analyses

Statistical analysis title	Proportions missed a dose over the last 3 days
Statistical analysis description: Logistic mixed model was fitted to compare binary outcome across treatment arms over time with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answer and strata].	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.793
Method	Logistic mixed model

Secondary: Adherence (parent response): Missed any dose since last clinic visit

End point title	Adherence (parent response): Missed any dose since last clinic visit
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End point description:

Parents/carers were asked if their child has missed any dose since last clinic visit

End point type	Secondary
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End point timeframe:

Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[59]	160 ^[60]		
Units: People				
Missed any dose since last clinic visit: Week 4	10	15		
Missed any dose since last clinic visit: Week 12	15	13		
Missed any dose since last clinic visit: Week 24	24	18		
Missed any dose since last clinic visit: Week 36	20	17		
Missed any dose since last clinic visit: Week 48	14	13		

Notes:

[59] - Denominator differed by study week: Week 4=143; Week 12=138; Week 24=137; Week 36=130; Week 48=124

[60] - Denominator differed by study week: Week 4=147; Week 12=143; Week 24=134; Week 36=134; Week 48=138

Statistical analyses

Statistical analysis title	Proportions missed any dose since last visit
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Statistical analysis description:

Logistic mixed model was fitted to compare binary outcome across treatment arms over time with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answer and strata].

Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
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Number of subjects included in analysis	318
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Analysis specification	Pre-specified
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Analysis type	other
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P-value	= 0.328
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Method	Logistic mixed model
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Secondary: Adherence (parent response): Adherence rating since the last clinic visit

End point title	Adherence (parent response): Adherence rating since the last clinic visit
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End point description:

Parents/carers were asked to complete adherence rating since the last clinic visit for their child

End point type	Secondary
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End point timeframe:

Collected at weeks 0, 4, 12, 24, 36, 48 and every 12 weeks thereafter to end of trial, defined as latest of trial censoring date (31July2020) or week 48 censoring date.

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[61]	160 ^[62]		
Units: People				
Week 4: Excellent	70	71		
Week 4: Very Good	61	63		
Week 4: Fair	7	6		
Week 4: Not recorded	5	7		
Week 12: Excellent	73	64		
Week 12: Very Good	49	67		
Week 12: Fair	10	6		
Week 12: Not that good	1	1		
Week 12: Not recorded	5	5		
Week 24: Excellent	64	66		
Week 24: Very Good	55	57		
Week 24: Fair	11	4		
Week 24: Not that good	1	1		
Week 24: Not recorded	6	6		
Week 36: Excellent	51	70		
Week 36: Very Good	61	50		
Week 36: Fair	14	6		
Week 36: Not that good	0	3		
Week 36: Not recorded	4	5		
Week 48: Excellent	40	47		
Week 48: Very Good	76	72		
Week 48: Fair	4	12		
Week 48: Not that good	1	0		
Week 48: Not recorded	3	7		

Notes:

[61] - Denominator differed by study week: Week 4=143; Week 12=138; Week 24=137; Week 36=130; Week 48=124

[62] - Denominator differed by study week: Week 4=147; Week 12=143; Week 24=134; Week 36=134; Week 48=138

Statistical analyses

Statistical analysis title	Comparing adherence rating since the last visit
Statistical analysis description: Ordered logistic mixed model was fitted to compare ordered outcome across treatment arms with a random effect for intercept and fixed effects for treatment group, post-randomisation study visits and adjustment covariates [baseline answers and strata].	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.411
Method	Ordered logistic mixed model

Secondary: Acceptability (participant response): Mood-related symptoms at week 48

End point title	Acceptability (participant response): Mood-related symptoms at week 48
End point description:	Participants were asked if they had mood-related symptoms
End point type	Secondary
End point timeframe:	Week 48

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[63]	154 ^[64]		
Units: People				
Dizziness or room spinning: Week 48	13	14		
Low mood or feeling sad often: Week 48	14	9		
Problems concentrating: Week 48	6	8		
Hurting or harming him/herself: Week 48	2	3		
Feeling worried often: Week 48	4	10		
Thinking life is not worth living: Week 48	3	3		
Feeling angry or aggressive often: Week 48	10	7		
Thinking about ending life: Week 48	2	4		

Notes:

[63] - Questionnaires completed at week 48

[64] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Comparing dizziness/room spinning at week 48
Statistical analysis description:	Comparing proportions reporting dizziness/room spinning at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.966
Method	Regression, Logistic

Statistical analysis title	Comparing low mood/feeling sad often at week 48
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Statistical analysis description:

Comparing proportions reporting low mood/feeling sad often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.19
Method	Regression, Logistic

Statistical analysis title	Comparing problems concentrating at week 48
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Statistical analysis description:

Comparing proportions reporting problems concentrating at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.545
Method	Regression, Logistic

Statistical analysis title	Comparing hurting/harming him/herself at week 48
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Statistical analysis description:

Comparing proportions reporting hurting/harming him/herself at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.682
Method	Regression, Logistic

Statistical analysis title	Comparing feeling worried often at week 48
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Statistical analysis description:

Comparing proportions reporting feeling worried often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.121
Method	Regression, Logistic

Statistical analysis title

Comparing thinking life is not worth living at w48

Statistical analysis description:

Comparing proportions reporting thinking life is not worth living at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9
Method	Regression, Logistic

Statistical analysis title

Comparing feeling angry/aggressive often at w48

Statistical analysis description:

Comparing proportions reporting feeling angry or aggressive often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.289
Method	Regression, Logistic

Statistical analysis title

Comparing thinking about ending life at week 48

Statistical analysis description:

Comparing proportions reporting thinking about ending life at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
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Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.46
Method	Regression, Logistic

Secondary: Acceptability (participant response): Sleep quality at week 48

End point title	Acceptability (participant response): Sleep quality at week 48
End point description:	
Participants were asked about the time taken to sleep and overall sleep quality, as well as if they had nightmares or vivid dreams	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148 ^[65]	154 ^[66]		
Units: People				
Time taken to sleep (Week 48): ≤15 minutes	71	73		
Time taken to sleep (Week 48): 15-30 minutes	42	44		
Time taken to sleep (Week 48): 30 minutes - 1 hour	14	12		
Time taken to sleep (Week 48): ≥1 hour	5	4		
Time taken to sleep (Week 48): Don't know	12	16		
Time taken to sleep (Week 48): Not recorded	4	5		
Nightmares (Week 48): Never	120	126		
Nightmares (Week 48): Infrequently	13	17		
Nightmares (Week 48): Occasionally	8	3		
Nightmares (Week 48): Frequently	1	1		
Nightmares (Week 48): Don't know	1	4		
Nightmares (Week 48): Not recorded	5	3		
Vivid dreams (Week 48): Never	89	98		
Vivid dreams (Week 48): Infrequently	23	17		
Vivid dreams (Week 48): Occasionally	18	20		
Vivid dreams (Week 48): Frequently	11	13		
Vivid dreams (Week 48): Don't know	2	3		
Vivid dreams (Week 48): Not recorded	5	3		
Sleep quality (Week 48): Very Good	70	66		
Sleep quality (Week 48): Good	53	58		
Sleep quality (Week 48): Fair	14	21		
Sleep quality (Week 48): Not that good	5	3		
Sleep quality (Week 48): Very bad	0	1		

Sleep quality (Week 48): Don't know	0	1		
Sleep quality (Week 48): Not recorded	6	4		

Notes:

[65] - Questionnaires completed at week 48

[66] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Comparing time taken to sleep at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.754
Method	Ordered logistic regression

Statistical analysis title	Comparing nightmares at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.821
Method	Ordered logistic regression

Statistical analysis title	Comparing vivid dreams at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.673
Method	Ordered logistic regression

Statistical analysis title	Comparing sleep quality at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.179
Method	Ordered logistic regression

Secondary: Acceptability (parent response): Mood-related symptoms at week 48

End point title	Acceptability (parent response): Mood-related symptoms at week 48
End point description:	Parents/carers were asked if their children had mood-related symptoms
End point type	Secondary
End point timeframe:	Week 48

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122 ^[67]	135 ^[68]		
Units: People				
Dizziness or room spinning: Week 48	5	6		
Low mood or feeling sad often: Week 48	12	14		
Problems concentrating: Week 48	1	5		
Hurting or harming him/herself: Week 48	0	1		
Feeling worried often: Week 48	2	6		
Thinking life is not worth living: Week 48	1	2		
Feeling angry or aggressive often: Week 48	8	10		
Thinking about ending life: Week 48	1	1		
Other: Week 48	0	0		

Notes:

[67] - Questionnaires completed at week 48

[68] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Comparing dizziness/room spinning at week 48
Statistical analysis description:	Comparing proportions reporting dizziness/room spinning at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.895
Method	Regression, Logistic

Statistical analysis title	Comparing low mood/feeling sad often at week 48
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Statistical analysis description:

Comparing proportions reporting low mood/feeling sad often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.839
Method	Regression, Logistic

Statistical analysis title	Comparing problems concentrating at week 48
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Statistical analysis description:

Comparing proportions reporting problems concentrating at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.108
Method	Regression, Logistic

Statistical analysis title	Comparing hurting/harming him/herself at week 48
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Statistical analysis description:

Comparing proportions reporting hurting/harming him/herself at week 48

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	Comparing feeling worried often at week 48
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Statistical analysis description:	
Comparing proportions reporting feeling worried often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.18
Method	Regression, Logistic

Statistical analysis title	Comparing thinking life is not worth living at w48
Statistical analysis description:	
Comparing proportions reporting thinking life is not worth living at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.612
Method	Regression, Logistic

Statistical analysis title	Comparing feeling angry/aggressive often at w48
Statistical analysis description:	
Comparing proportions reporting feeling angry or aggressive often at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.904
Method	Regression, Logistic

Statistical analysis title	Comparing thinking about ending life at week 48
Statistical analysis description:	
Comparing proportions reporting thinking about ending life at week 48 (logistic regression p-value adjusted for baseline answer and stratification factors)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.945
Method	Regression, Logistic

Secondary: Acceptability (parent response): Sleep quality at week 48

End point title	Acceptability (parent response): Sleep quality at week 48
End point description: Parents/carers were asked questions about their children: time taken to sleep and overall sleep quality, as well as if their children had nightmares or vivid dreams	
End point type	Secondary
End point timeframe: Week 48	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122 ^[69]	135 ^[70]		
Units: People				
Time taken to sleep (Week 48): ≤15 minutes	57	65		
Time taken to sleep (Week 48): 15-30 minutes	33	39		
Time taken to sleep (Week 48): 30 minutes - 1 hour	15	7		
Time taken to sleep (Week 48): ≥1 hour	2	0		
Time taken to sleep (Week 48): Don't know	11	20		
Time taken to sleep (Week 48): Not recorded	4	4		
Nightmares (Week 48): Never	84	94		
Nightmares (Week 48): Infrequently	11	7		
Nightmares (Week 48): Occasionally	4	2		
Nightmares (Week 48): Frequently	1	0		
Nightmares (Week 48): Don't know	19	26		
Nightmares (Week 48): Not recorded	3	6		
Vivid dreams (Week 48): Never	71	78		
Vivid dreams (Week 48): Infrequently	15	9		
Vivid dreams (Week 48): Occasionally	3	10		
Vivid dreams (Week 48): Frequently	5	1		
Vivid dreams (Week 48): Don't know	25	31		
Vivid dreams (Week 48): Not recorded	3	6		
Sleep quality (Week 48): Very Good	48	57		
Sleep quality (Week 48): Good	57	57		
Sleep quality (Week 48): Fair	8	13		
Sleep quality (Week 48): Not that good	2	1		
Sleep quality (Week 48): Very bad	1	0		

Sleep quality (Week 48): Don't know	2	1		
Sleep quality (Week 48): Not recorded	4	6		

Notes:

[69] - Questionnaires completed at week 48

[70] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Comparing time taken to sleep at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.276
Method	Ordered logistic regression

Statistical analysis title	Comparing nightmares at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.128
Method	Ordered logistic regression

Statistical analysis title	Comparing vivid dreams at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.511
Method	Ordered logistic regression

Statistical analysis title	Comparing sleep quality at week 48
Statistical analysis description: Ordered logistic regression p-value adjusted for baseline answers and strata.	

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.554
Method	Ordered logistic regression

Secondary: How did taking INSTI+DRV/r make things for you compared to previous meds (participant response)?

End point title	How did taking INSTI+DRV/r make things for you compared to previous meds (participant response)? ^[71]
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End point description:

At end of study visit participants were asked: How did taking INSTI+DRV/r make things for you compared to previous meds? No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[71] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	157 ^[72]			
Units: People				
A lot easier	52			
A little easier	13			
No difference	14			
A little more difficult	2			
Not recorded	76			

Notes:

[72] - Questionnaires completed. Only answered by those in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall, how did you feel whilst taking INSTI+DRV/r compared with pre-study meds (participant response)?

End point title	Overall, how did you feel whilst taking INSTI+DRV/r compared with pre-study meds (participant response)? ^[73]
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End point description:

At end of study visit participants were asked: Overall, how did you feel whilst taking INSTI+DRV/r compared with pre-study meds. No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[73] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	157 ^[74]			
Units: People				
I felt better before the study	2			
I felt better on Tivicay or Elvitegravir and Prezi	55			
No difference	25			
Not recorded	75			

Notes:

[74] - Questionnaires completed. Only answered by those in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Would you be happy to stay on INSTI+DRV/r (participant response)?

End point title	Would you be happy to stay on INSTI+DRV/r (participant response)? ^[75]
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End point description:

At end of study visit participants were asked: Would you be happy to stay on INSTI+DRV/r? No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[75] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	157 ^[76]			
Units: People				
Yes	66			
No	11			
Not sure	2			
NA: I have already restarted pre-study meds	2			
Not recorded	76			

Notes:

[76] - Questionnaires completed. Only answered by those in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: How did taking INSTI+DRV/r make things for you compared to your child's previous meds (parent response)?

End point title	How did taking INSTI+DRV/r make things for you compared to your child's previous meds (parent response)? ^[77]
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End point description:

At end of study visit parent/carer were asked: How did taking INSTI+DRV/r make things for you compared to your child's previous meds. No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[77] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	116 ^[78]			
Units: People				
A lot easier	38			
A little easier	8			
No difference	8			
A little more difficult	6			
Not recorded	56			

Notes:

[78] - Questionnaires completed. Only answered by participant's parents/carers in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall, how did your child feel whilst taking INSTI+DRV/r compared with your child's pre-study meds (parent response)?

End point title	Overall, how did your child feel whilst taking INSTI+DRV/r compared with your child's pre-study meds (parent response)? ^[79]
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End point description:

At end of study visit parents/carers were asked: Overall, how did your child feel whilst taking INSTI+DRV/r compared with your child's pre-study meds. No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[79] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	116 ^[80]			
Units: People				
Felt better before the study	1			
Better on Tivicay/Elvitegravir+Prezista/Norvir	41			
No difference	18			
Not recorded	56			

Notes:

[80] - Questionnaires completed. Only answered by participant's parents/carers in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Would you be happy for your child to stay on INSTI+DRV/r (parent response)?

End point title	Would you be happy for your child to stay on INSTI+DRV/r (parent response)? ^[81]
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End point description:

At end of study visit parents/carers were asked: Would you be happy for your child to stay on INSTI+DRV/r? No statistical analyses for this end point.

End point type	Secondary
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End point timeframe:

End of study visit defined as the participant's study exit visit, which takes place on/after trial censoring date (31 July 2020).

Notes:

[81] - 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: Questionnaire only answered by participants or parents/carers of participants in INSTI+DRV/r arm. This is not applicable to SOC arm.

End point values	Intervention (Arm 1) - INSTI+DRV/r			
Subject group type	Reporting group			
Number of subjects analysed	116 ^[82]			
Units: People				
Yes	49			
No	9			
Not sure	1			
NA: My child has already restarted pre-study meds	2			

Not recorded	55			
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Notes:

[82] - Questionnaires completed. Only answered by participant's parents/carers in INSTI+DRV/r arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in PedsQL Total Score from randomisation to week 48 (participant response)

End point title	Mean change in PedsQL Total Score from randomisation to week 48 (participant response)
End point description: Reporting mean change from the global baseline value (across both arms). PedsQL total Score is composed of 23 items comprising all 4 dimensions (Physical, Emotional, Social and School Functioning Scales)	
End point type	Secondary
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151 ^[83]	154 ^[84]		
Units: PedsQL score				
arithmetic mean (standard error)	3.5 (\pm 0.8)	4.3 (\pm 0.7)		

Notes:

[83] - Questionnaires completed at week 48

[84] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of PedsQL Total Score at week 48, adjusting for baseline PedsQL Total Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.458
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	1.3

Secondary: Mean change in PedsQL Physical Health Score from randomisation to week 48 (participant response)

End point title	Mean change in PedsQL Physical Health Score from randomisation to week 48 (participant response)
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151 ^[85]	154 ^[86]		
Units: PedsQL score				
arithmetic mean (standard error)	1.9 (± 0.8)	2.9 (± 0.8)		

Notes:

[85] - Questionnaires completed at week 48

[86] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of PedsQL Physical Health Score at week 48, adjusting for baseline PedsQL Physical Health Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.402
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	1.3

Secondary: Mean change in PedsQL Psychosocial Health Score from randomisation to week 48 (participant response)

End point title	Mean change in PedsQL Psychosocial Health Score from randomisation to week 48 (participant response)
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End point description:

Reporting mean change from the global baseline value (across both arms). PedsQL Psychosocial Health score is composed of 15 items comprising 3 dimensions (Emotional, Social, and School Functioning Scales).

End point type	Secondary
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End point timeframe:

Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151 ^[87]	154 ^[88]		
Units: PedsQL score				
arithmetic mean (standard error)	4.3 (± 0.9)	5.0 (± 0.8)		

Notes:

[87] - Questionnaires completed at week 48

[88] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
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Statistical analysis description:

Linear regression of PedsQL Psychosocial Health Score at week 48, adjusting for baseline PedsQL Psychosocial Health Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.575
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1.7

Secondary: Mean change in PedsQL Total Score from randomisation to week 48 (parent response)

End point title	Mean change in PedsQL Total Score from randomisation to week 48 (parent response)
End point description: Reporting mean change from the global baseline value (across both arms). PedsQL total Score is composed of 23 items comprising all 4 dimensions (Physical, Emotional, Social and School Functioning Scales)	
End point type	Secondary
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119 ^[89]	126 ^[90]		
Units: PedsQL score				
arithmetic mean (standard error)	4.1 (± 1.0)	2.6 (± 1.0)		

Notes:

[89] - Questionnaires completed at week 48

[90] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of PedsQL Total Score at week 48, adjusting for baseline PedsQL Total Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.364
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	4

Secondary: Mean change in PedsQL Physical Health Score from randomisation to week 48 (parent response)

End point title	Mean change in PedsQL Physical Health Score from randomisation to week 48 (parent response)
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End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Secondary
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119 ^[91]	126 ^[92]		
Units: PedsQL score				
arithmetic mean (standard error)	2.4 (± 1.1)	0.6 (± 1.1)		

Notes:

[91] - Questionnaires completed at week 48

[92] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
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Statistical analysis description:

Linear regression of PedsQL Physical Health Score at week 48, adjusting for baseline PedsQL Physical Health Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)

Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.268
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.7

Secondary: Mean change in PedsQL Psychosocial Health Score from randomisation to week 48 (parent response)

End point title	Mean change in PedsQL Psychosocial Health Score from randomisation to week 48 (parent response)
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End point description:

Reporting mean change from the global baseline value (across both arms). PedsQL Psychosocial Health score is composed of 15 items comprising 3 dimensions (Emotional, Social, and School Functioning Scales).

End point type	Secondary
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End point timeframe:

Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119 ^[93]	126 ^[94]		
Units: PedsQL score				
arithmetic mean (standard error)	4.9 (\pm 1.1)	3.7 (\pm 1.1)		

Notes:

[93] - Questionnaires completed at week 48

[94] - Questionnaires completed at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of PedsQL Psychosocial Health Score at week 48, adjusting for baseline PedsQL Psychosocial Health Score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.518
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	3.9

Secondary: Serious adverse events reported to end of trial

End point title	Serious adverse events reported to end of trial
End point description:	
End point type	Secondary
End point timeframe: Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[95]	160 ^[96]		
Units: People				
SAEs reported	4	4		
No SAEs reported	154	156		

Notes:

[95] - 4 participants reported 4 SAEs

[96] - 4 participants reported 5 SAEs.

Statistical analyses

Statistical analysis title	Serious adverse event incidence rate ratio
Statistical analysis description: SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode (Major depression + Suicidal ideation). Each hospital admission is reported as a separate SAE. Poisson regression adjusted for stratification factors and event clustering within individuals.	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.763
Method	Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	3.22

Statistical analysis title	Time to first serious adverse event
Statistical analysis description: SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode (Major depression + Suicidal ideation). Each hospital admission is reported as a separate SAE. Cox regression analysis examining time to first serious adverse event adjusted for stratification factors.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.993
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	4.02

Statistical analysis title	Proportion of participants with ≥ 1 SAEs reported
Statistical analysis description: Comparison of proportion of participants with ≥ 1 SAEs between arms (Chi-squared test).	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.986
Method	Chi-squared

Secondary: Grade 3 or 4 adverse events reported to end of trial

End point title	Grade 3 or 4 adverse events reported to end of trial
End point description: Note: grade 3/4 clinical or laboratory AEs include any events reported at grade 3 or 4. These events may be part of SAEs or be reported as ART modifying AEs or notable events.	
End point type	Secondary
End point timeframe: Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[97]	160 ^[98]		
Units: People				
Grade 3 or 4 AEs reported	13	19		
No Grade 3 or 4 AEs reported	145	141		

Notes:

[97] - 13 participants reported 13 Grade 3 or 4 AEs.

[98] - 19 participants reported 25 Grade 3 or 4 AEs.

Statistical analyses

Statistical analysis title	Grade 3/4 adverse event incidence rate ratio
Statistical analysis description: Grade 3 or 4 clinical and laboratory adverse events. Poisson regression adjusted for stratification factors and event clustering within individuals.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

	2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.079
Method	Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.08

Statistical analysis title	Time to first grade 3 or 4 AE
Statistical analysis description:	
Grade 3 or 4 clinical and laboratory adverse events. Cox regression analysis examining time to first grade 3 or 4 AE adjusted for stratification factors.	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.237
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.32

Statistical analysis title	Proportion of participants with ≥ 1 Grade 3/4 AEs
Statistical analysis description:	
Comparison of proportion of participants with ≥ 1 Grade 3/4 AEs between arms (Chi-squared test).	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28
Method	Chi-squared

Secondary: ART modifying AEs (all grades) reported to end of trial

End point title	ART modifying AEs (all grades) reported to end of trial
End point description:	
ART modifying AEs (all grades) include all events that are ART modifying. These events may be part of SAEs or be reported as grade 3/4 AEs or notable events. ART modifying AEs are analysed as episodes, with all components of the same clinical ART modifying AE presented as one episode (Behaviour disorder + Decreased appetite + Depression).	
End point type	Secondary
End point timeframe:	
Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158 ^[99]	160 ^[100]		
Units: People				
ART modifying AEs reported	4	4		
No ART modifying AEs reported	154	156		

Notes:

[99] - 4 participants reported 4 ART modifying AEs.

[100] - 4 participants reported 6 ART modifying AEs

Statistical analyses

Statistical analysis title	ART modifying AE incidence rate ratio
Statistical analysis description:	
ART modifying AEs are defined as events reported at any grade leading to treatment modification including events leading to treatment interruption/stop. Poisson regression adjusted for stratification factors and event clustering within individuals.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.575
Method	Poisson regression
Parameter estimate	Rate Ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	2.67

Statistical analysis title	Time to first ART modifying AE
Statistical analysis description:	
Cox regression analysis examining time to first ART modifying AE adjusted for stratification factors.	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.959
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	4.15

Statistical analysis title	Proportion with ≥ 1 ART modifying AEs
Statistical analysis description: Comparison of proportion of participants with ≥ 1 ART modifying AEs between arms (Chi-squared test).	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.986
Method	Chi-squared

Other pre-specified: Mean change in BMI from randomisation to week 24

End point title	Mean change in BMI from randomisation to week 24
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe: Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: kg/m ²				
arithmetic mean (standard error)	0.83 (\pm 0.1)	0.33 (\pm 0.1)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of BMI at week 24, adjusting for baseline BMI and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.7

Other pre-specified: Mean change in BMI from randomisation to week 48

End point title	Mean change in BMI from randomisation to week 48
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145 ^[101]	153 ^[102]		
Units: kg/m2				
arithmetic mean (standard error)	1.25 (± 0.1)	0.59 (± 0.1)		

Notes:

[101] - Participants with a measurement at week 48

[102] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of BMI at week 48, adjusting for baseline BMI and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1

Other pre-specified: Mean change in BMI-for-age z-score from randomisation to week 24

End point title	Mean change in BMI-for-age z-score from randomisation to week 24
End point description:	Reporting mean change from the global baseline value (across both arms).
End point type	Other pre-specified
End point timeframe:	Randomisation and week 24 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: z-score				
arithmetic mean (standard error)	0.19 (± 0.0)	0.03 (± 0.0)		

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description:	Linear regression of BMI-for-age z-score at week 24, adjusting for baseline BMI-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.3

Other pre-specified: Mean change in BMI-for-age z-score from randomisation to week 48

End point title	Mean change in BMI-for-age z-score from randomisation to week 48
End point description:	Reporting mean change from the global baseline value (across both arms).
End point type	Other pre-specified
End point timeframe:	Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145 ^[103]	153 ^[104]		
Units: z-score				
arithmetic mean (standard error)	0.23 (± 0.0)	0.01 (± 0.0)		

Notes:

[103] - Participants with a measurement at week 48

[104] - Participants with a measurement at week 48

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	Linear regression of BMI-for-age z-score at week 48, adjusting for baseline BMI-for-age z-score and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC). British 1990 Reference data was used for calculation of BMI, weight and height z-scores. This reference data covers the full age range (0–23 years) of SMILE participants.
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.3

Other pre-specified: Notable events reported to end of trial

End point title	Notable events reported to end of trial
End point description:	Notable events include Covid-19 events, Liver events, Pregnancies and Suicidal ideation reported at any grade. These events may be part of SAEs or reported as grade 3 or 4 AEs or ART modifying AEs.
End point type	Other pre-specified
End point timeframe:	Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	160		
Units: People				
Pregnancy	1	2		
Suicidal ideation	0	1		
Drug induced liver injury	2	1		
COVID-19 contact	1	0		
No notable events reported	154	156		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in CD8% from randomisation to week 24

End point title	Mean change in CD8% from randomisation to week 24
End point description:	Reporting mean change from the global baseline value (across both arms).
End point type	Other pre-specified

End point timeframe:
Randomisation and week 24 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 ^[105]	125 ^[106]		
Units: Percentage				
arithmetic mean (standard error)	-0.7 (\pm 0.4)	-0.4 (\pm 0.4)		

Notes:

[105] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

[106] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of CD8% at week 24, adjusting for baseline CD8% and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.627
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.7

Other pre-specified: Mean change in CD8% from randomisation to week 48

End point title	Mean change in CD8% from randomisation to week 48
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe: Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121 ^[107]	130 ^[108]		
Units: Percentage				
arithmetic mean (standard error)	-0.5 (± 0.5)	-0.6 (± 0.5)		

Notes:

[107] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

[108] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	
Linear regression of CD8% at week 48, adjusting for baseline CD8% and stratification factors.	
Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.82
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.5

Other pre-specified: Mean change in CD8 count from randomisation to week 24

End point title	Mean change in CD8 count from randomisation to week 24
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe:	
Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 ^[109]	125 ^[110]		
Units: cells/mm3				
arithmetic mean (standard error)	-20.1 (± 19.2)	-3.9 (± 18.8)		

Notes:

[109] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

[110] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description:	
Linear regression of CD8 count at week 24, adjusting for baseline CD8 count and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.565
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.7
upper limit	37.6

Other pre-specified: Mean change in CD8 count from randomisation to week 48

End point title	Mean change in CD8 count from randomisation to week 48
End point description:	
Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe:	
Randomisation and week 48 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121 ^[111]	130 ^[112]		
Units: Percentage				
arithmetic mean (standard error)	2.6 (± 22.8)	-25.7 (± 22.1)		

Notes:

[111] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

[112] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description: Linear regression of CD8 count at week 48, adjusting for baseline CD8 count and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.373
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	28.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.5
upper limit	91.5

Other pre-specified: Mean change in CD4%/CD8% ratio from randomisation to week 24

End point title	Mean change in CD4%/CD8% ratio from randomisation to week 24
End point description: Reporting mean change from the global baseline value (across both arms).	
End point type	Other pre-specified
End point timeframe: Randomisation and week 24 visit	

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115 ^[113]	125 ^[114]		
Units: Ratio				
arithmetic mean (standard error)	0.00 (± 0.03)	0.02 (± 0.03)		

Notes:

[113] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

[114] - Participants with a measurement at week 24. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 24
Statistical analysis description: Linear regression of CD4%/CD8% ratio at week 24, adjusting for baseline CD4%/CD8% ratio and stratification factors. Presenting difference in mean change from baseline to week 24 between arms (INSTI+DRV/r-SOC)	
Comparison groups	Standard of care (Arm 2) v Intervention (Arm 1) - INSTI+DRV/r

Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.482
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0

Other pre-specified: Mean change in CD4%/CD8% ratio from randomisation to week 48

End point title	Mean change in CD4%/CD8% ratio from randomisation to week 48
End point description:	Reporting mean change from the global baseline value (across both arms).
End point type	Other pre-specified
End point timeframe:	Randomisation and week 48 visit

End point values	Intervention (Arm 1) - INSTI+DRV/r	Standard of care (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121 ^[115]	129 ^[116]		
Units: Ratio				
arithmetic mean (standard error)	-0.04 (± 0.03)	0.03 (± 0.03)		

Notes:

[115] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

[116] - Participants with a measurement at week 48. CD8 tests are optional, according to feasibility.

Statistical analyses

Statistical analysis title	Difference in mean change from baseline to week 48
Statistical analysis description:	Linear regression of CD4%/CD8% ratio at week 48, adjusting for baseline CD4%/CD8% ratio and stratification factors. Presenting difference in mean change from baseline to week 48 between arms (INSTI+DRV/r-SOC)
Comparison groups	Intervention (Arm 1) - INSTI+DRV/r v Standard of care (Arm 2)

Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any time from randomisation to end of trial [defined as latest of trial censoring date (31July2020) or week 48 censoring date (week 54 date)]

Adverse event reporting additional description:

For non-serious adverse events, we reported grade 3 or 4 clinical or laboratory adverse events, ART-modifying adverse events (any grade) and notable events, excluding those meeting criteria for serious adverse events (SAE). Notable events include Covid-19 events, Liver events, Pregnancies and Suicidal ideation.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	INSTI+DRV/r (Arm 1)
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Reporting group description:

Arm 1. NRTI-sparing regimen: Once daily integrase inhibitor (INSTI) + darunavir/ritonavir (DRV/r)

Reporting group title	Standard of care (Arm 2)
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Reporting group description:

Arm 2. Standard of care (continuing triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI)

Serious adverse events	INSTI+DRV/r (Arm 1)	Standard of care (Arm 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 158 (2.53%)	4 / 160 (2.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatitis acute	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy	Additional description: SAE and Severe CDC stage B event. Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression	Additional description: SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode (Major depression + Suicidal ideation). Each hospital admission is a separate SAE. Causality assessment reported as per site investigator's decision.		
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation	Additional description: SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode (Major depression + Suicidal ideation). Each hospital admission is a separate SAE. Causality assessment reported as per site investigator's decision.		
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pilonidal cyst	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium falciparum infection	Additional description: Serious adverse event causality assessment to treatment is reported as per site investigator's decision, which cannot be overruled by any other clinical reviewers.		

subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
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: 0 %

Non-serious adverse events	INSTI+DRV/r (Arm 1)	Standard of care (Arm 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 158 (7.59%)	18 / 160 (11.25%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 158 (0.63%)	1 / 160 (0.63%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 158 (1.90%)	0 / 160 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 158 (0.00%)	3 / 160 (1.88%)	
occurrences (all)	0	3	
Blood calcium decreased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 160 (0.63%)	
occurrences (all)	0	1	
Low density lipoprotein increased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 160 (0.00%)	
occurrences (all)	1	0	
Pregnancy test positive			

subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	1 / 160 (0.63%) 1	
Injury, poisoning and procedural complications Exposure to SARS-CoV-2 subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Nervous system disorders Meningism subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	1 / 160 (0.63%) 1	
Pregnancy, puerperium and perinatal conditions Abortion incomplete subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	1 / 160 (0.63%) 1	
Pregnancy subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	1 / 160 (0.63%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	3 / 160 (1.88%) 3	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 158 (0.00%) 0	4 / 160 (2.50%) 6	
Psychiatric disorders			

Adjustment disorder with mixed disturbance of emotion and conduct subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Behaviour disorder subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	1 / 160 (0.63%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 158 (0.63%) 1	0 / 160 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2017	<p>Protocol amendment #1 was due to a temporary halt following the withdrawal of Elvitegravir (EVG). The notification of temporary suspension was submitted to any countries that had already received approval for the trial. The notification dates will vary from country to country. Protocol v2.0 was drafted and released on 27 July 2017. The amendment dates vary from country to country, but the first approval for v2.0 was granted on 30 August 2017 in Belgium. For countries that have enrolled participants, approval for v2.0 was first granted on 25 September 2017 in Spain. Protocol v2.0 replaced EVG with another INSTI called Dolutegravir (DTG).</p> <p>Note that because the protocol amendment dates will vary from country to country we have entered it as the protocol v2.0 date of 24 July 2017.</p>
05 August 2020	<p>Protocol amendment #2 was for protocol v4.0. This was to incorporate the continuation phase for countries that did not have access to SMILE IMP after end of main trial (LPLV in main trial was 01 October 2020). It also included details on COVID-19 management and additional information on DTG pregnancy management due to the safety alert initially released in May 2018. This updated protocol was only submitted in countries that did not have access to SMILE IMP through their National programme at the end of the trial. These countries were South Africa, Uganda, Thailand and Ukraine. Protocol v4.0 was released globally on 18 Sept 2020, however the dates of submission will vary from country to country. Therefore, we have entered it as the protocol v4.0 date of 05 August 2020.</p> <p>Additional Continuation phase information: In order to ensure that all SMILE participants had equal access to the SMILE regimen (at least for a further 12 months after the end of the main trial), the Sponsor incorporated a continuation phase "access programme" into the trial protocol and this was submitted for approval in the aforementioned countries. Pharmaceutical companies providing dolutegravir and darunavir for SMILE were happy to provide the drug at no extra cost for a further 12 month period but required notification of any reportable safety events in participants receiving drug through this access programme. No other data was collected during this period and no further analyses were carried out using continuation phase data as the continuation phase was purely to ensure access to the SMILE regimen".</p> <p>The LPLV date in the continuation phase was 17 November 2021. This is the global end of trial date for SMILE.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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06 October 2016	Gilead withdrew Elvitegravir from the market as a single entity leading to temporary suspension of recruitment on 6 October 2016 (date PIs received notification of suspension of recruitment). Enrolments re-started on 12 February 2018 once Elvitegravir was replaced by Dolutegravir. First approval of protocol version 2.0 for restart was 30 August 2017 in Belgium. For countries that have enrolled participants, approval for v2.0 was first granted on 25 September 2017 in Spain.	12 February 2018
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Notes:

Limitations and caveats

None reported