Clinical trial results:
BREATHER (PENTA 16): Short-cycle therapy (SCT) (5 days on/ 2 days off) in young people with chronic HIV-infection

Summary

EudraCT number	2009-012947-40
Trial protocol	IE GB ES DK BE DE
Global end of trial date	

Results information

Result version number	v1
This version publication date	04 February 2017
First version publication date	04 February 2017

Trial information

Trial identification

Sponsor protocol code	PENTA16

Additional study identifiers

ISRCTN number	ISRCTN97755073
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The PENTA foundation
Sponsor organisation address	Torre della Ricerca Pediatrica Corso Stati Uniti 4, Padova, Italy, 35127
Public contact	University College London, University College London, penta.mrcctu@ucl.ac.uk
Scientific contact	University College London, University College London, penta.mrcctu@ucl.ac.uk

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	Interim
Date of interim/final analysis	31 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of the BREATHER trial is to evaluate the role of Short-Cycle Therapy (SCT) in the management of HIV-infected young people who have responded well to antiretroviral therapy (ART) and to determine whether young people with chronic HIV infection undergoing Short-Cycle Therapy of five days on ART and two days off maintain the same level of viral load suppression as those on continuous therapy, over 48 weeks.

Protection of trial subjects:

In order to assess the safety of the SCT strategy, a pilot study was carried out in 32 young people, who were seen on the Monday morning following having Saturday and Sunday off treatment. Their viral loads were assessed on this visit and the main trial did not commense until the IDMC had confirmed they had no saftey concerns as a result of the pilot phase.

Background therapy:

Every young person were on a first-line HAART regimen containing at least 2 NRTI/NtRTIs and EFV.

Evidence for comparator:

Current WHO guidelines recommend a first-line ART regimen containing 2 NRTI/NtRTIs and EFV for treatment of HIV in children.

Actual start date of recruitment	01 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Thailand: 36
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Uganda: 70
Country: Number of subjects enrolled	Ukraine: 20
Worldwide total number of subjects	199
EEA total number of subjects	48

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)	53
Adolescents (12-17 years)	104
Adults (18-64 years)	42
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	225[1]
Number of subjects completed	199

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Protocol deviation: 21
Reason: Number of subjects	Car crash prevented them making randomsation visit: 1
Reason: Number of subjects	Unreliable attendance: 1

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: 225 young people were screened, but 199 randomised. Reasons for not randomising are documented here.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Continuous therapy

Arm description:

Patients randomised to continuing their ART strategy, taking ART every day.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Short Cycle Therapy

Arm description:

Patients take their ART as normal for 5 days a week, with a break at the weekends, taking no ART for 2 days every week.

The only product enterred here is Efavirenz, as all young people in the trial were on Efavirenz. However, it is not the drug that is being investigated in this trial, it is the strategy in which the ART regimen is taken.

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

Dosage and administration details:

Dosed as perscribed by the clinician.

Number of subjects in period 1	Continuous therapy	Short Cycle Therapy
Started	100	99
Completed	99	99
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Continuous therapy
Reporting group description:	
Patients randomised to continuing their ART strategy, taking ART every day.	
Reporting group title	Short Cycle Therapy
Reporting group description:	
Patients take their ART as normal for 5 days a week, with a break at the weekends, taking no ART for 2 days every week. The only product enterred here is Efavirenz, as all young people in the trial were on Efavirenz. However, it is not the drug that is being investigated in this trial, it is the strategy in which the ART regimen is taken.	

Reporting group values	Continuous therapy	Short Cycle Therapy	Total
Number of subjects	100	99	199
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)	25	28	53
Adolescents (12-17 years)	55	49	104
Adults (18-64 years)	20	22	42
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	14.4	13.7	
inter-quartile range (Q1-Q3)	12 to 17.5	11.7 to 17.7	-
Gender categorical Units: Subjects			
Female	52	42	94
Male	48	57	105
Route of infection			
Mode of transmission of HIV			
Units: Subjects			
Vertical	90	90	180
Sexual contact	7	7	14
Blood product	2	1	3
Unknown	1	1	2
Ethnic origin			
Ethnicity			
Units: Subjects			
White	17	24	41
Black	54	58	112
Mixed black/white	4	0	4

Asian	22	15	37
Other	3	2	5
CDC stage			
CDC stage event at randomisation			
Units: Subjects			
Stage N	10	16	26
Stage A	25	25	50
Stage B	43	45	88
Stage C	21	13	34
Missing	1	0	1
Classes of drugs exposed to			
Classes of drugs exposed to by randomisation			
Units: Subjects			
NRTIs, NNRTIs and PIs	12	17	29
NRTIs and NNRTIs only	88	82	170
Baseline regimen first regimen			
Is the baseline regimen their first ART regimen?			
Units: Subjects			
Yes	42	40	82
No	58	59	117
Young person questionnaire - how will taking weekends off make things for you?			
Question from acceptability questionnaire answerred by the young person.			
Units: Subjects			
A lot easier	0	50	50
A little easier	0	20	20
No difference	0	8	8
A little more difficult	0	2	2
A lot more difficult	0	0	0
Question not answerred	100	19	119
Carer questionnaire - how will stopping meds at weekend make things for the young person?			
Question from acceptability questionnaire answerred by the carer.			
Units: Subjects			
A lot easier	0	45	45
A little easier	0	16	16
No difference	0	7	7
A little more difficult	0	4	4
A lot more difficult	0	1	1
Question not answerred	100	26	126
Weight			
Weight at randomisation			
Units: kilogram(s)			
median	45.1	45.5	
inter-quartile range (Q1-Q3)	33.9 to 55.7	33.1 to 56.2	-
CD4%			
Mean of CD4% from screening and randomisation visit.			
Units: percent			
median	34	34.5	
inter-quartile range (Q1-Q3)	29.5 to 38.1	29.3 to 39	-

Absolute CD4 count			
Mean of CD4 count from screening and randomisation visit.			
Units: cells/microlitre			
median	747.3	722.5	
inter-quartile range (Q1-Q3)	575.3 to 972.8	581 to 965	-
Creatinine			
Creatinine at randomisation			
Units: milligram(s)/decilitre			
median	0.6	0.5	
inter-quartile range (Q1-Q3)	0.5 to 0.7	0.4 to 0.7	-
Total bilirubin			
Total bilirubin at randomisation			
Units: milligram(s)/decilitre			
median	0.3	0.2	
inter-quartile range (Q1-Q3)	0.2 to 0.4	0.2 to 0.3	-
Alkaline phosphatase			
Alkaline phosphatase at randomisation			
Units: milligram(s)/decilitre			
median	224	260.5	
inter-quartile range (Q1-Q3)	130 to 320	136 to 347	-
Aspartate transaminase			
Aspartate transaminase at randomisation			
Units: unit(s)/litre			
median	25	25	
inter-quartile range (Q1-Q3)	20 to 30	19 to 34	-
Alanine transaminase			
Alanine transaminase at randomisation			
Units: unit(s)/litre			
median	17.5	18	
inter-quartile range (Q1-Q3)	14 to 25	12 to 26	-
Glucose			
Glucose at randomisation			
Units: milligram(s)/decilitre			
median	86.5	86.4	
inter-quartile range (Q1-Q3)	81.5 to 90.9	82.9 to 91.9	-
Triglycerides			
Triglycerides at randomisation			
Units: milligram(s)/decilitre			
median	81	74.8	
inter-quartile range (Q1-Q3)	61.7 to 121	54.8 to 102.7	-
LDL Cholesterol			
LDL Cholesterol at randomisation			
Units: milligram(s)/decilitre			
median	85.6	89	
inter-quartile range (Q1-Q3)	76 to 108	78.1 to 107.4	-
HDL Cholesterol			
HDL Cholesterol at randomisation			
Units: milligram(s)/decilitre			
median	54.9	51	
inter-quartile range (Q1-Q3)	46.3 to 68.2	42.5 to 62	-
Total cholesterol			
Total cholesterol at randomisation			

Units: milligram(s)/decilitre			
median	164.1	158.2	
inter-quartile range (Q1-Q3)	147.3 to 181.5	142.9 to 181	-
Haemoglobin			
Haemoglobin at randomisation			
Units: gram(s)/decilitre			
median	13.2	13.2	
inter-quartile range (Q1-Q3)	12.3 to 14.2	12.2 to 14	-
MCV			
MCV at randomisation			
Units: femtolitres			
median	92	94	
inter-quartile range (Q1-Q3)	86 to 100.5	87.3 to 100.5	-
White cell count			
White cell count at randomisation			
Units: /litre			
median	5	4.6	
inter-quartile range (Q1-Q3)	4 to 6.3	3.9 to 6	-
Lymphocytes			
Lymphocytes at randomisation			
Units: /litre			
median	2.2	2.2	
inter-quartile range (Q1-Q3)	1.7 to 2.9	1.7 to 2.6	-
Neutrophils			
Neutrophils at randomisation			
Units: /litre			
median	1.9	1.9	
inter-quartile range (Q1-Q3)	1.2 to 3.4	1.4 to 2.9	-
Platelets			
Platelet count at randomisation			
Units: /litre			
median	292.5	293	
inter-quartile range (Q1-Q3)	247.5 to 352.5	244 to 352	-

End points

End points reporting groups

Reporting group title	Continuous therapy
Reporting group description:	
Patients randomised to continuing their ART strategy, taking ART every day.	
Reporting group title	Short Cycle Therapy
Reporting group description:	
Patients take their ART as normal for 5 days a week, with a break at the weekends, taking no ART for 2 days every week. The only product enterred here is Efavirenz, as all young people in the trial were on Efavirenz. However, it is not the drug that is being investigated in this trial, it is the strategy in which the ART regimen is taken.	

Primary: Virological failure (>=50c/ml confirmed).

End point title	Virological failure (>=50c/ml confirmed).
End point description:	
The primary endpoint was a confirmed viral load >=50c/ml within 54 weeks of randomisation.	
End point type	Primary
End point timeframe:	
Any time from randomisation to 48(+6) weeks after randomisation.	

End point values	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: People				
Reached endpoint	7	6		
Did not reach endpoint	93	93		

Statistical analyses

Statistical analysis title	Primary analysis - diff in adj. KM estimates
Statistical analysis description:	
Difference in adjusted (for stratification factors) Kaplan-Meier survival function estimates at 54 weeks after randomisation.	
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.012

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.073
upper limit	0.049

Notes:

[1] - Non-inferiority margin = 12%.

Calculated SCT arm survival function - CT arm survival function, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Secondary analysis - unadjusted diff

Statistical analysis description:

Difference in Kaplan-Meier survival function estimates at 54 weeks after randomisation.

Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Mean difference (final values)
Point estimate	-0.011
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.068
upper limit	0.046

Notes:

[2] - Non-inferiority margin = 12%.

Calculated SCT arm survival function - CT arm survival function, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Secondary analysis - crude diff

Statistical analysis description:

Difference in proportion of YP with confirmed VL>=50c/ml.

Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	-0.009
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.067
upper limit	0.048

Notes:

[3] - Non-inferiority margin = 12%.

Calculated proportion of YP with virological failure in the SCT arm - proportion of YP with virological failure in the CT arm, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Secondary analysis - unadj. Cox model

Statistical analysis description:

Cox model examining time to confirmed viral load >=50c/ml

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.755 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.34
upper limit	2.1

Notes:

[4] - Non-significant difference between arms.

Statistical analysis title	Secondary analysis - adj. Cox model

Statistical analysis description:

Cox model examining time to confirmed viral load >=50c/ml, adjusting for stratification factors.

Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.743 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.33
upper limit	2.08

Notes:

[5] - Non-significant difference between arms.

Secondary: Virological failure (>=400c/ml confirmed).

End point title	Virological failure (>=400c/ml confirmed).

End point description:

Confirmed viral load >=400c/ml within 54 weeks of randomisation.

End point type	Secondary

End point timeframe:

Any time from randomisation to 48(+6) weeks after randomisation.

End point values	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: People				
Reached endpoint	4	2		
Did not reach endpoint	96	97		

Statistical analyses

Statistical analysis title	Diff. in adj. KM estimates

Statistical analysis description:

Difference in adjusted (for stratification factors) Kaplan-Meier survival function estimates at 54 weeks after randomisation.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Mean difference (final values)
Point estimate	-0.021
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.062
upper limit	0.019

Notes:

[6] - Calculated SCT arm survival function - CT arm survival function, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Unadj. diff. in KM estimates

Statistical analysis description:

Difference in Kaplan-Meier survival function estimates at 54 weeks after randomisation.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.061
upper limit	0.02

Notes:

[7] - Calculated SCT arm survival function - CT arm survival function, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Crude diff. in proportion

Statistical analysis description:

Difference in proportion of YP with confirmed VL>=400c/ml.

Comparison groups	Continuous therapy v Short Cycle Therapy

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.06
upper limit	0.02

Notes:

[8] - Calculated proportion of YP with virological failure in the SCT arm - proportion of YP with virological failure in the CT arm, so if the upper bound of the 90% confidence interval was <0.12, the results were consistent with non-inferiority of SCT compared with CT.

Statistical analysis title	Unadj. Cox model

Statistical analysis description:

Cox model examining time to confirmed viral load >=400c/ml

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.12
upper limit	2.01

Statistical analysis title	Adj. Cox model

Statistical analysis description:

Cox model examining time to confirmed viral load >=400c/ml, adjusting for stratification factors.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.399
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.12
upper limit	2

Secondary: SCT change strategy to continuous therapy

End point title	SCT change strategy to continuous therapy[9]

End point description:

Any young person that changed strategy from SCT to return to taking daily ART, and reasons for changing.

The protocol states that young people should return to continuous therapy if they experience the primary endpoint, or have 3 viral load "blips" >=50c/ml, which have a subsequent VL reading that is <50c/ml.

End point type	Secondary

End point timeframe:

Any time from randomisation to week 48(+6).

Notes:

[9] - 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: This is only applicable to those randomised to SCT and therefore cannot be reported for those on CT, as they are all already taking their ART every day.

End point values	Short Cycle Therapy			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: People				
Due to reaching primary endpoint	6			
Due to 3 unconfirmed blips	0			
Due to other reasons	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in ART regimen

End point title	Changes in ART regimen

End point description:

Number of individuals on a different ART regimen at week 48 to at week 0.

End point type	Secondary

End point timeframe:

Randomisation to week 48(+6).

End point values	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[10]	99		
Units: People				
Change in ART regimen	9	3		
No change in ART regimen	90	96		

Notes:

[10] - 1 young person lost to follow up before week 48 visit

Statistical analyses

Statistical analysis title	Snapshot comparison at week 48 visit

Statistical analysis description:

Fisher's exact test comparing number of young people still on their randomised regimen at week 48 from each arm.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	198
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.104
Method	Fisher exact

Secondary: Young people with major resistance mutations - any class

End point title	Young people with major resistance mutations - any class

End point description:

Resistance tests were performed on everyone that reached the primary endpoint. "Major mutation" defined as in Johnson et. al., 2013, Topics in antiviral medicine.

End point type	Secondary

End point timeframe:

Randomisation to week 48(+6)

End point values	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[11]	6[12]		
Units: People				
Major mutations present	5	2		
No major mutations present	1	1		
Test failed to amplify (insufficient viral load)	1	3		

Notes:

[11] - Only performed on young people that reached the primary endpoint.

[12] - Only performed on young people that reached the primary endpoint.

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change in CD4% at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[13]	93[14]		
Units: percent				
arithmetic mean (standard error)	0.1 (± 0.4)	0.2 (± 0.4)		

Notes:

[13] - All patients with a reading at week 48 and week 0.

[14] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression
Statistical analysis description:	
Linear regression of CD4% at week 48, adjusting for randomised arm, baseline CD4% and stratification factors. Presenting mean difference between arms.	
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.76
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.3

Secondary: Mean change in absolute CD4 count at week 48 from randomisation

End point title	Mean change in absolute CD4 count at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[15]	92[16]		
Units: cells/microlitre				
arithmetic mean (standard error)	-21.6 (± 21.1)	-34.2 (± 20.9)		

Notes:

[15] - All patients with a reading at week 48 and week 0.

[16] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of absolute CD4 count at week 48, adjusting for randomised arm, baseline absolute CD4 count and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.68
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.9
upper limit	46.9

Secondary: Mean change in Creatinine at week 48 from randomisation

End point title	Mean change in Creatinine at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[17]	93[18]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Notes:

[17] - All patients with a reading at week 48 and week 0.

[18] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of creatinine at week 48, adjusting for randomised arm, baseline creatinine and stratification factors. Presenting mean difference between arms.

Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.42
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1

Secondary: Mean change in bilirubin at week 48 from randomisation

End point title	Mean change in bilirubin at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[19]	91[20]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)		

Notes:

[19] - All patients with a reading at week 48 and week 0.

[20] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of bilirubin at week 48, adjusting for randomised arm, baseline bilirubin and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.45
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1

Secondary: Mean change in Alkaline phosphatase at week 48 from randomisation

End point title	Mean change in Alkaline phosphatase at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[21]	90[22]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-17.4 (± 9.3)	-24.8 (± 9.3)		

Notes:

[21] - All patients with a reading at week 48 and week 0.

[22] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of Alkaline phosphatase at week 48, adjusting for randomised arm, baseline Alkaline phosphatase and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.77
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.3
upper limit	21

Secondary: Mean change in Aspartate transaminase at week 48 from randomisation

End point title	Mean change in Aspartate transaminase at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[23]	87[24]		
Units: unit(s)/litre				
arithmetic mean (standard error)	0.5 (± 1)	-1.2 (± 1)		

Notes:

[23] - All patients with a reading at week 48 and week 0.

[24] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of aspartate transaminase at week 48, adjusting for randomised arm, baseline aspartate transaminase and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.22
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	1

Secondary: Mean change in Alanine transaminase at week 48 from randomisation

End point title	Mean change in Alanine transaminase at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[25]	92[26]		
Units: unit(s)/litre				
arithmetic mean (standard error)	1.8 (± 1.3)	-0.4 (± 1.3)		

Notes:

[25] - All patients with a reading at week 48 and week 0.

[26] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.
Statistical analysis description:	
Linear regression of alanine transaminase at week 48, adjusting for randomised arm, baseline alanine transaminase and stratification factors. Presenting mean difference between arms.	
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.23
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	1.4

Secondary: Mean change in Glucose at week 48 from randomisation	
End point title	Mean change in Glucose at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[27]	90[28]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	1.7 (± 1.1)	1.6 (± 1.1)		

Notes:

[27] - All patients with a reading at week 48 and week 0.

[28] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.
Statistical analysis description:	
Linear regression of glucose at week 48, adjusting for randomised arm, baseline glucose and stratification factors. Presenting mean difference between arms.	
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.93
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	3

Secondary: Mean change in Triglycerides at week 48 from randomisation	
End point title	Mean change in Triglycerides at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[29]	93[30]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-2.8 (± 4.8)	6.3 (± 4.8)		

Notes:

[29] - All patients with a reading at week 48 and week 0.

[30] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of triglycerides at week 48, adjusting for randomised arm, baseline triglycerides and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	22.2

Secondary: Mean change in LDL Cholesterol at week 48 from randomisation

End point title	Mean change in LDL Cholesterol at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[31]	89[32]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-0.3 (± 1.6)	1.3 (± 1.7)		

Notes:

[31] - All patients with a reading at week 48 and week 0.

[32] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of LDL cholesterol at week 48, adjusting for randomised arm, baseline LDL cholesterol and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.52
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	6.1

Secondary: Mean change in VLDL cholesterol at week 48 from randomisation

End point title	Mean change in VLDL cholesterol at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[33]	49[34]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-1.9 (± 1.1)	-3.1 (± 1.2)		

Notes:

[33] - All patients with a reading at week 48 and week 0.

[34] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of VLDL cholesterol at week 48, adjusting for randomised arm, baseline VLDL cholesterol and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.44
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.9

Secondary: Mean change in HDL cholesterol at week 48 from randomisation

End point title	Mean change in HDL cholesterol at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[35]	92[36]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-0.5 (± 1)	-2.1 (± 1)		

Notes:

[35] - All patients with a reading at week 48 and week 0.

[36] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of HDL cholesterol at week 48, adjusting for randomised arm, baseline HDL cholesterol and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	1.2

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of HDL cholesterol at week 48, adjusting for randomised arm, baseline HDL cholesterol and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.28
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	1.3

Secondary: Mean change in total cholesterol at week 48 from randomisation	
End point title	Mean change in total cholesterol at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[37]	93[38]		
Units: milligram(s)/decilitre				
arithmetic mean (standard error)	-2.2 (± 2.1)	0.6 (± 2)		

Notes:

[37] - All patients with a reading at week 48 and week 0.

[38] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of total cholesterol at week 48, adjusting for randomised arm, baseline total cholesterol and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.35
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	8.5

Secondary: Mean change in Haemoglobin at week 48 from randomisation

End point title	Mean change in Haemoglobin at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[39]	95[40]		
Units: gram(s)/decilitre				
arithmetic mean (standard error)	0 (± 0.1)	0.1 (± 0.1)		

Notes:

[39] - All patients with a reading at week 48 and week 0.

[40] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of haemoglobin at week 48, adjusting for randomised arm, baseline haemoglobin and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.37
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.4

Secondary: Mean change in MCV at week 48 from randomisation

End point title	Mean change in MCV at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[41]	94[42]		
Units: femtolitres				
arithmetic mean (standard error)	-1.6 (± 0.5)	-3.6 (± 0.5)		

Notes:

[41] - All patients with a reading at week 48 and week 0.

[42] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of MCV at week 48, adjusting for randomised arm, baseline MCV and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001 [43]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-0.6

Notes:

[43] - Significicant difference between arms - higher MCV in the continuous therapy arm.

Secondary: Mean change in white blood cell count at week 48 from randomisation

End point title	Mean change in white blood cell count at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[44]	95[45]		
Units: /litre				
arithmetic mean (standard error)	0.1 (± 0.1)	0.4 (± 0.1)		

Notes:

[44] - All patients with a reading at week 48 and week 0.

[45] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of white blood cell count at week 48, adjusting for randomised arm, baseline white blood cell count and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.09
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.7

Secondary: Mean change in Lymphocyte count at week 48 from randomisation

End point title	Mean change in Lymphocyte count at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[46]	91[47]		
Units: /litre				
arithmetic mean (standard error)	0 (± 0.5)	0.7 (± 0.5)		

Notes:

[46] - All patients with a reading at week 48 and week 0.

[47] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of lymphocyte count at week 48, adjusting for randomised arm, baseline lymphocyte count and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.34
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	2.1

Secondary: Mean change in Neutrophil count at week 48 from randomisation

End point title	Mean change in Neutrophil count at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[48]	91[49]		
Units: /litre				
arithmetic mean (standard error)	0.1 (± 0.1)	0.4 (± 0.1)		

Notes:

[48] - All patients with a reading at week 48 and week 0.

[49] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of neutrophil count at week 48, adjusting for randomised arm, baseline neutrophil count and stratification factors. Presenting mean difference between arms.

Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.12
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.7

Secondary: Mean change in platelet count at week 48 from randomisation

End point title	Mean change in platelet count at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[50]	95[51]		
Units: /litre				
arithmetic mean (standard error)	7.4 (± 6.6)	-13.4 (± 6.5)		

Notes:

[50] - All patients with a reading at week 48 and week 0.

[51] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.
Statistical analysis description:	
Linear regression of platelet count at week 48, adjusting for randomised arm, baseline platelet count and stratification factors. Presenting mean difference between arms.	
Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03 [52]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.1
upper limit	-2.1

Notes:

[52] - Significant difference between the arms, higher platelet count in the continuous therapy arm.

Secondary: Young person questionnaire - how did taking weekends off make things for you?

End point title	Young person questionnaire - how did taking weekends off make things for you?[53]
End point description:	
This questionnaire was only completed in the SCT arm.	
End point type	Secondary
End point timeframe:	
Week 48 assessment/time of switch to continuous therapy/ last main trial visit (if after week 48).	

Notes:

[53] - 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: Acceptability questionnaires only completed by those randomised to SCT.

End point values	Short Cycle Therapy			
Subject group type	Reporting group			
Number of subjects analysed	99[54]			
Units: People				
Lot easier	67			
Little easier	14			
No difference	7			
Little more difficult	0			
Lot more difficult	2			
Question not answerred	9			

Notes:

[54] - Only answerred by those randomised to SCT arm

Statistical analyses

No statistical analyses for this end point

Secondary: Carer questionnaire - how did stopping meds at weekend make things for the young person?

End point title	Carer questionnaire - how did stopping meds at weekend make things for the young person?[55]

End point description:

This questionnaire was only asked in the SCT arm.

End point type	Secondary

End point timeframe:

Week 48 assessment/time of switch to continuous therapy/ last main trial visit (if after week 48).

Notes:

[55] - 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: Acceptability questionnaires only completed by those randomised to SCT.

End point values	Short Cycle Therapy			
Subject group type	Reporting group			
Number of subjects analysed	99[56]			
Units: People				
Lot easier	49			
Little easier	9			
No difference	3			
Little more difficult	0			
Lot more difficult	0			
Question not answerred	38			

Notes:

[56] - Only answerred by those randomised to the SCT arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence- Missed Doses at Last Visit

End point title	Adherence- Missed Doses at Last Visit

End point description:

Participants were asked if they missed any doses since the last visit.

End point type	Secondary

End point timeframe:

Collected at Week 4, 12, 24, 36, and 48.

End point values	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: Number of Questionnaires				
Missed doses since last visit: Week 4	15	23		
Missed doses since last visit: Week 12	19	23		
Missed doses since last visit: Week 24	20	25		
Missed doses since last visit: Week 36	15	22		
Missed doses since last visit: Week 48	18	20		

Statistical analyses

Statistical analysis title	Comparison of missed doses at week 4
Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Fisher exact

Statistical analysis title	Comparison of missed doses at week 12
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.593
Method	Fisher exact

Statistical analysis title	Comparison of missed doses at week 24

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488
Method	Fisher exact

Statistical analysis title	Comparison of missed doses at week 38
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193
Method	Fisher exact

Statistical analysis title	Comparison of missed doese at week 48
Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.854
Method	Fisher exact

Other pre-specified: Mean change in CD8% at week 48 from randomisation	
End point title	Mean change in CD8% at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[57]	89[58]		
Units: percent				
arithmetic mean (standard error)	-0.3 (± 0.5)	-0.5 (± 0.5)		

Notes:

[57] - All patients with a reading at week 48 and week 0.

[58] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of CD8% at week 48, adjusting for randomised arm, baseline CD8% and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.2

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

End point title	Mean change in absolute CD8 count at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[59]	89[60]		
Units: cells/microlitre				
arithmetic mean (standard error)	-14.8 (± 24.5)	-22.1 (± 23.8)		

Notes:

[59] - All patients with a reading at week 48 and week 0.

[60] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of absolute CD8 count at week 48, adjusting for randomised arm, baseline absolute CD8 count and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.85
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.5
upper limit	61.7

Other pre-specified: Mean change in CD3% at week 48 from randomisation	
End point title	Mean change in CD3% at week 48 from randomisation
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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[61]	88[62]		
Units: percent				
arithmetic mean (standard error)	-0.7 (± 0.7)	-0.7 (± 0.7)		

Notes:

[61] - All patients with a reading at week 48 and week 0.

[62] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.
Statistical analysis description:	
Linear regression of CD3% at week 48, adjusting for randomised arm, baseline CD3% and stratification factors. Presenting mean difference between arms.	
Comparison groups	Short Cycle Therapy v Continuous therapy
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.99
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.9

Other pre-specified: Mean change in absolute CD3 count at week 48 from randomisation

End point title	Mean change in absolute CD3 count at week 48 from randomisation

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	Continuous therapy	Short Cycle Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[63]	88[64]		
Units: cells/microlitre				
arithmetic mean (standard error)	-25.9 (± 49.5)	-56.6 (± 48.4)		

Notes:

[63] - All patients with a reading at week 48 and week 0.

[64] - All patients with a reading at week 48 and week 0.

Statistical analyses

Statistical analysis title	Linear regression.

Statistical analysis description:

Linear regression of absolute CD3 count at week 48, adjusting for randomised arm, baseline absolute CD3 count and stratification factors. Presenting mean difference between arms.

Comparison groups	Continuous therapy v Short Cycle Therapy
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.72
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-25.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-163.7
upper limit	112.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Randomisation to 54 weeks after randomisation.	
Adverse event reporting additional description:	
For non-serious adverse events we reported grade three or four adverse clinical or laboratory adverse events.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Continuous therapy
Reporting group description:	
Patients randomised to continuing their ART strategy, taking ART every day.	
Reporting group title	Short Cycle Therapy
Reporting group description:	
Patients take their ART as normal for 5 days a week, with a break at the weekends, taking no ART for 2 days every week.	

Serious adverse events	Continuous therapy	Short Cycle Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 100 (3.00%)	6 / 99 (6.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Kaposi's sarcoma AIDS related			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation (following contusion of chest)			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation (Collapsed)			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Measles			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosyphilis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Continuous therapy	Short Cycle Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 100 (12.00%)	8 / 99 (8.08%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Blood calcium decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Low density lipoprotein increased			
subjects affected / exposed	1 / 100 (1.00%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Neutrophil count decreased			

subjects affected / exposed	6 / 100 (6.00%)	2 / 99 (2.02%)	
occurrences (all)	6	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Kaposi's Sarcoma AIDS related			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia repair			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Hemiparesis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Collapse/suspected seizure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Lipohypertrophy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Measles			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	The TSC recommended that the participants are followed for 2 years after completion of the main trial (long term follow up).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported