Clinical trial results:
A phase II baseline versus treatment study to determine the efficacy of raltegravir (ISENTRESS) in preventing progression of relapsing remitting multiple sclerosis as determined by gadolinium-enhanced MRI

Summary

EudraCT number	2012-004847-61
Trial protocol	GB
Global end of trial date	10 June 2015

Results information

Result version number	v1 (current)
This version publication date	25 June 2016
First version publication date	25 June 2016
Summary attachment (see zip file)	INSPIRE end of study report (Inspire End of Study Report May 26.doc)

Trial information

Trial identification

Sponsor protocol code	008717QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02104661
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
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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	12 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2014
Global end of trial reached?	Yes
Global end of trial date	10 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess whether treatment with raltegravir in patients with active MS has the effect of reducing the total number or rate of development of new or recurrent Gd-enhanced lesions on brain MRI over the period of treatment, compared to baseline.

Protection of trial subjects:

All participants provided written informed consent before any study specific assessments were performed. Participants were given ample time for consideration before consenting to take part. Participants were made aware of their right to withdraw from the study at any time for any reason. The investigator also had the right to withdraw participants from the study. The total time on the study for enrolled participants was six months, which was considered to be an ethically acceptable timeframe for patients who are in the early stages of RRMS as this is the time limit before they meet Association of British Neurologists (ABN) criteria for currently licensed disease modifying treatment.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable for this open label single arm study

Actual start date of recruitment	01 February 2013
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	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participants were recruited at the Clinical Research Centre of the Royal London Hospital and were drawn prevalently from the catchment area of greater London. Participants were also referred to the site by six Patient Identification Centres (PICs). Recruitment into the study started in May 2013. The last patient was screened in June 2014.

Pre-assignment

Screening details:

A total of 31 participants were screened, of these 8 had no evidence of Gd enhancing lesions in their baseline MRI and were screen failed. Of the 23 participants who were recruited into the study 3 were withdrawn prior to starting the treatment phase; one at the request of the participant and the remaining two due to MS relapse.

Pre-assignment period milestones

Number of subjects started	31
Intermediate milestone: Number of subjects	Observation period: 23
Number of subjects completed	20

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No gd-enhancing lesions in MRI: 8
Reason: Number of subjects	MS relapse: 2
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable for this open label single arm trial.

Arms

Arm title	Treatment

Arm description:

Single arm open label

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

Dosage and administration details:

400mg twice a day administrated as the potassium salt in a film coated tablet

Number of subjects in period 1[1]	Treatment
Started	20
Completed	20

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 31 subjects screened, 20 received treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	20	20	
Age categorical			
Patients eligible for the study were between 18-55 years of age. PP mean age baseline 41.62yrs (31.15-52.99); ITT mean age baseline 40.73yrs (31.15-52.99).			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (18-55 years)	20	20	
Age continuous			
PP Mean age baseline 41.62yrs (31.15-52.99) ITT Mean age baseline 40.73yrs (31.15-52.99)			
Units: years			
arithmetic mean	40.73		
standard deviation	± 6.98	-	
Gender categorical			
PP 12 females (75%), 4 males (25%). ITT 14 females (70%), 6 males (30%).			
Units: Subjects			
Female	14	14	
Male	6	6	
Height			
PP mean height 168.91cm (156.0-180.0) ITT mean height 169.04cm (156.0-183.0) There are only reported height values for n=18.			
Units: cm			
arithmetic mean			
standard deviation	±	-	
Weight			
PP n=14; mean weight 77.9; (51.9-108.3) ITT n=18; mean weight 78.73; (51.9-109.7) Weight was not recorded for 2 subjects.			
Units: Kg			
arithmetic mean			
standard deviation	±	-	
Baseline EDSS			
PP n=16; mean EDSS 2.25; (0.0-3.5)			

ITT n=20; mean EDSS 2.4; (0.0-4.0)			
Units: score arithmetic mean standard deviation	±	-	
Number of relapses in the past year			
PP n= 16; mean 1.44; sd= 0.63 (1.0-3.0) ITT n= 20; mean 1.50; sd= 0.61 (0.0-4.0)			
Units: number of relapses arithmetic mean standard deviation	±	-	

Subject analysis sets

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

4 subjects were excluded from per protocol (PP) analysis due to concomitant medications (2 has steroids/immunosuppressants at screening and 2 had proton pump inhibitors during the study).
PP 12 females (75%), 4 males (25%). Mean age baseline 41.62yrs (31.15-52.99); mean height 168.91cm (156.0-180.0); mean weight 77.9Kg (51.9-108.3); mean EDSS 2.25 (0.0-3.5); mean no. relapses past year 1.44 (1-3)

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All 20 subjects who completed the study were includedin the ITT analysis.
ITT 14 females (70%), 6 males (30%). Mean age baseline 40.73yrs (31.15-52.99); mean height 169.04cm (156.0-183.0); mean weight 78.73Kg (51.9-109.7); mean EDSS 2.4 (0.0-4.0); mean no. relapses past year 1.5 (1-3)

Subject analysis set title	Flexible per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

Flexible PP sample n=18. Two subjects were excluded for all visits, one subject had visits seven and eight excluded, and one subject had just visit eight excluded.

Reporting group values	Per protocol	ITT	Flexible per protocol
Number of subjects	16	20	18
Age categorical			
Patients eligible for the study were between 18-55 years of age. PP mean age baseline 41.62yrs (31.15-52.99); ITT mean age baseline 40.73yrs (31.15-52.99).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18-55 years)	16	20	18
Age continuous			
PP Mean age baseline 41.62yrs (31.15-52.99) ITT Mean age baseline 40.73yrs (31.15-52.99)			

Units: years			
arithmetic mean	41.62	40.73	
standard deviation	± 7.49	± 6.98	±

Gender categorical			
PP 12 females (75%), 4 males (25%). ITT 14 females (70%), 6 males (30%).			
Units: Subjects			
Female	12	14	
Male	4	6	
Height			
PP mean height 168.91cm (156.0-180.0) ITT mean height 169.04cm (156.0-183.0) There are only reported height values for n=18.			
Units: cm			
arithmetic mean	168.91	169.04	
standard deviation	± 8	± 8.61	±
Weight			
PP n=14; mean weight 77.9; (51.9-108.3) ITT n=18; mean weight 78.73; (51.9-109.7) Weight was not recorded for 2 subjects.			
Units: Kg			
arithmetic mean	77.9	78.73	
standard deviation	± 18.45	± 19.04	±
Baseline EDSS			
PP n=16; mean EDSS 2.25; (0.0-3.5) ITT n=20; mean EDSS 2.4; (0.0-4.0)			
Units: score			
arithmetic mean	2.25	2.4	
standard deviation	± 1	± 1.03	±
Number of relapses in the past year			
PP n= 16; mean 1.44; sd= 0.63 (1.0-3.0) ITT n= 20; mean 1.50; sd= 0.61 (0.0-4.0)			
Units: number of relapses			
arithmetic mean	1.44	1.5	
standard deviation	± 0.63	± 0.61	±

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Single arm open label	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
4 subjects were excluded from per protocol (PP) analysis due to concomitant medications (2 has steroids/immunosuppressants at screening and 2 had proton pump inhibitors during the study). PP 12 females (75%), 4 males (25%). Mean age baseline 41.62yrs (31.15-52.99); mean height 168.91cm (156.0-180.0); mean weight 77.9Kg (51.9-108.3); mean EDSS 2.25 (0.0-3.5); mean no. relapses past year 1.44 (1-3)	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All 20 subjects who completed the study were includedin the ITT analysis. ITT 14 females (70%), 6 males (30%). Mean age baseline 40.73yrs (31.15-52.99); mean height 169.04cm (156.0-183.0); mean weight 78.73Kg (51.9-109.7); mean EDSS 2.4 (0.0-4.0); mean no. relapses past year 1.5 (1-3)	
Subject analysis set title	Flexible per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Flexible PP sample n=18. Two subjects were excluded for all visits, one subject had visits seven and eight excluded, and one subject had just visit eight excluded.	

Primary: Total T1 Gd-enhancing lesions in brain MRI scans

End point title	Total T1 Gd-enhancing lesions in brain MRI scans
End point description:	
Within-patient average no. new Gd-enh lesions observed on serial T1-weighted brain MRI scans. Counts of new or recurrent Gd-enh lesions appearing on brain T1-weighted MRI. These counts are available at each of visits 2 to 8 in the majority of patients. ITT n=20 'flexible' PP n=18. 2 patients were excluded for all visits, 1 patient had just visits 7 and 8 excluded, and 1 had visit 8 excluded. PP n=16, 4 patients had all their visits excluded. There were missing counts for 1patient at visit 3, 1 at visit 5, and missing counts for 2 at visit 6. Lesion outcomes provide no statistical evidence consistent with an effect of raltegravir. This is not because of lack of power: changes were not only non-significant statistically, but also generally clinically small (including both small reductions and small increases). For the most substantial change, a reduction in persisting T1 Gd lesions in the PP sample, the decrease before intervention was greater than that afterwards	
End point type	Primary
End point timeframe:	
Visit two (enrolment) is excluded from analysis, which covers visits three, four and five "before-", and six, seven and eight "after-" medication was first dispensed.	

End point values	Treatment	Per protocol	ITT	Flexible per protocol
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	16	20	18
Units: Number and ratio of lesions				
arithmetic mean (full range (min-max))				
Number of T1 gd-enhancing lesions before	8.65 (0 to 32)	7.5 (0 to 32)	8.65 (0 to 32)	7.28 (0 to 32)
Number of T1 Gd-enhancing lesions after	9.05 (0 to 31)	7 (0 to 31)	9.05 (0 to 31)	6.83 (0 to 31)
Number of T1 Gd-enh lesions within patient change	0.12 (-2.67 to 3.33)	-0.18 (-2.67 to 2.33)	0.12 (-2.67 to 3.33)	-0.16 (-2.67 to 2.33)
Ratio of T1 Gd-Enh lesions within patient change	0.88 (0.15 to 3.33)	0.81 (0.15 to 3.33)	0.88 (0.15 to 3.33)	0.83 (0.15 to 3.33)

Statistical analyses

Statistical analysis title	Mixed effect Poisson regression model

Statistical analysis description:

A mixed effect Poisson regression model with before/after indicator, adjusting for the (log) enrolment visit value

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.681 [2]
Method	Regression, Linear
Parameter estimate	Rate ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.29

Notes:

[1] - The analyses compare the mean rate after vs before. The potential gradients of change over the three-month before vs after periods were also compared. For all three samples above there was no significant change in the after vs before gradients of monthly lesion accrual: P-values were respectively P=0.659, 0.429 and 0.463 for ITT, flexible PP and PP.

[2] - Est rate ratio after vs before: 1.04 (95% CI .85, 1.29); represents 4% non-significant incr lesions/month in after period, weighted ITT rate ratio 1.03
Simple non-parametric Wilcoxon sign rank test within-patient changes non-significant, P=0.646

Statistical analysis title	Mixed effect Poisson regression model

Statistical analysis description:

A mixed effect Poisson regression model with before/after indicator, adjusting for the (log) enrolment visit value

Comparison groups	Treatment v Flexible per protocol

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.714 [3]
Method	Regression, Linear
Parameter estimate	rate ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.22

Notes:

[3] - 5% non-significant decrease in rate. This is in close agreement with the summary weighted rate ratio of 0.92. The p-value from the simple non-parametric Wilcoxon sign rank test of changes is non-significant, P=0.183.

Statistical analysis title	Mixed effect Poisson regression model

Statistical analysis description:

A mixed effect Poisson regression model with before/after indicator, adjusting for the (log) enrolment visit value

Comparison groups	Treatment v Per protocol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.577 [4]
Method	Regression, Linear
Parameter estimate	rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.2

Notes:

[4] - Non-significant 7% decrease. This is similar to the summary weighted rate ratio of 0.92. The p-value from the simple non-parametric Wilcoxon sign rank test of changes is also non-significant, P=0.197.

Primary: Persisting T1 Gd-enhancing brain MRI lesions

End point title	Persisting T1 Gd-enhancing brain MRI lesions

End point description:

End point type	Primary

End point timeframe:

Visits 3, 4 and 5 (before) and 6, 7 and 8 (after medication was first dispensed).

End point values	Treatment	Per protocol	ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	16	20	
Units: Change in gradient of rate ratio				
arithmetic mean (full range (min-max))				
Monthy rate before	1.46 (0 to 7.67)	1.53 (0 to 7.67)	1.46 (0 to 7.67)	
Monthly rate after	1.35 (0 to 5.67)	1.19 (0 to 5.67)	1.35 (0 to 5.67)	
Within patient change in rate	-0.11 (-2 to 1.67)	-0.34 (-2 to 0.67)	-0.11 (-2 to 1.67)	

Statistical analyses

Statistical analysis title	Poisson regression
Statistical analysis description:	
A mixed effect Poisson regression model with before/after indicator.	
Comparison groups	Treatment v Per protocol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.16 [5]
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.1

Notes:

[5] - The rate ratio was estimated as 0.78 (95% CI:0.55, 1.10) P=0.160, a non-significant reduction. There was no significant change in gradient in the PP (0.762). In this PP sample the rate of reduction after was slightly lower than that before.

Statistical analysis title	Poisson regression
Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.652 [6]
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.26

Notes:

[6] - The rate ratio was estimated as 0.93 (95% CI .69, 1.26), P=0.652, a slight and non-significant reduction in persisting lesions.

Primary: New T1 Gd enhancing brain MRI lesions

End point title	New T1 Gd enhancing brain MRI lesions

End point description:

Rates in each 3-months period.

End point type	Primary

End point timeframe:

Before (visits 3, 4, 5) vs After (visits 6, 7, 8).

End point values	Treatment	Per protocol	ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	16	20	
Units: Monthly rate of new lesions				
arithmetic mean (full range (min-max))				
Monthly rate before	1.46 (0 to 7.67)	1.53 (0 to 7.67)	1.46 (0 to 7.67)	
Monthly rate after	1.35 (0 to 5.67)	1.19 (0 to 5.67)	1.35 (0 to 5.67)	
Within patient change in monthly rate	-0.11 (-2 to 1.67)	-0.34 (-2 to 0.67)	-0.11 (-2 to 1.67)	

Statistical analyses

Statistical analysis title	Poisson regression model

Statistical analysis description:

A mixed effect Poisson regression model with before/after indicator estimates the rate ratio after vs before as 1.16 (95% CI 0.87, 1.55), P=0.314; this represents a slight and non-significant increase in new lesions per month in the 'after' period. The above analyses compare the mean rate after vs before. The gradients of change over the three-month before vs after periods were also compared.

Comparison groups	Treatment v Per protocol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.456
Method	Regression, Linear

Notes:

[7] - There was no significant change in the after vs before gradients of monthly lesion accrual in the PP (P=0.137).

Statistical analysis title	Poisson regression model

Statistical analysis description:

A mixed effect Poisson regression model with before/after indicator estimates the rate ratio after vs before as 1.16 (95% CI 0.87, 1.55), P=0.314; this represents a slight and non-significant increase in new lesions per month in the 'after' period. This analysis compares the mean rate after vs before. The gradients of change over the three-month before vs after periods were also compared.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.314 [8]
Method	Regression, Linear
Parameter estimate	Slope
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.55

Notes:

[8] - There was no significant change in the after vs before gradients of monthly lesion accrual in the ITT (P=0.562) analysis.

Secondary: New or enlarging T2 weighted lesions on brain MRI

End point title	New or enlarging T2 weighted lesions on brain MRI

End point description:

For T2 lesions (where the only 'after' observation is visit 8, so no comparison is possible for the two 'flexible PP' patients), only ITT and PP are given. Within-patient ratios averaged on log scale before back transforming, substituting 0.1 for zero counts. Weighted mean ratios pooled on log scale by weighting for lesion counts.

End point type	Secondary

End point timeframe:

Counts of new or enlarging T2-weighted lesions at visits five (before) and eight (after).

End point values	Treatment	Per protocol	ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	16	20	
Units: Number and ratio of lesions				
arithmetic mean (full range (min-max))				
Number of T2 lesions before	4.45 (0 to 17)	3.13 (0 to 9)	4.45 (0 to 17)	
Number of T2 lesions after	4.65 (0 to 20)	3.31 (0 to 13)	4.65 (0 to 20)	
Within patient T2 lesions count change	0.2 (-4 to 5)	0.19 (-4 to 5)	0.2 (-4 to 5)	
Within patient T2 lesions count ratio	1.47 (0.2 to 10)	1.64 (0.2 to 10)	1.47 (0.2 to 10)	

Statistical analyses

Statistical analysis title	Wilcoxon sign rank test
Comparison groups	Treatment v Per protocol

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.462 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Non-significant: Wilcoxon sign rank test of the within-patient changes was P= 0.462 for PP analysis.

Statistical analysis title	Wilcoxon sign rank test
Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.472 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Non-significant: Wilcoxon sign rank test of the within-patient changes was P=0.472 for ITT analysis.

Secondary: Inflammatory markers

End point title	Inflammatory markers

End point description:

Statistical analysis performed on three inflammatory markers:

Interleukin-8 (IL-8), or chemokine (C-X-C motif) ligand 8, CXCL8, is a chemokine produced by macrophages and other cell types. IL-8 secretion is increased by oxidant stress, which thereby cause the recruitment of inflammatory cells and induces a further increase in oxidant stress mediators, making it a key parameter in localized inflammation. Reported in pg/mL Unit.

Serum CD163 (a soluble form of the receptor exists in plasma, commonly denoted sCD163. It is generated by ectodomain shedding of the membrane bound receptor. sCD163 is upregulated in a large range of inflammatory diseases). Reported in ng/mL Unit.

Human C-reactive protein (HCRP), CRP is used mainly as a marker of inflammation.
For HCRP, three measurements above the measureable threshold were assigned values of 10000 ng/ml. The largest measurable HCRP value in the dataset is 9492.25. Reported in ng/mL Unit.

End point type	Secondary

End point timeframe:

Changes in mean at visits 3, 4, and 5 (before) and 6, 7, and 8 (after).

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Changes in mean after - before				
arithmetic mean (standard deviation)				
IL-8	0.82 (± 2.12)	0.82 (± 2.12)		
CD163	18.67 (± 38.18)	18.67 (± 38.18)		
HCRP	535.82 (± 1244)	535.82 (± 1244)		

Statistical analyses

Statistical analysis title	IL-8 One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1 [11]
Method	One sample t-test

Notes:

[11] - Non significant

Statistical analysis title	IL-8 Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.47 [12]
Method	Mixed models analysis

Notes:

[12] - Non significant

Statistical analysis title	IL-8 Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.193 [13]
Method	Change in gradient

Notes:

[13] - Non significant

Statistical analysis title	CD163 one sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.041 [14]
Method	One sample t-test

Notes:

[14] - Significant decline changes to a significant positive gradient. The gradient change is significant in both ITT and PP.

Statistical analysis title	CD163 Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04 [15]
Method	Mixed models analysis

Notes:

[15] - Significant decline changes to a significant positive gradient. The gradient change is significant in both ITT and PP.

Statistical analysis title	CD163 Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018 [16]
Method	Change in gradient

Notes:

[16] - Significant.

Statistical analysis title	HCRP one sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.069 [17]
Method	One sample t-test

Notes:

[17] - Significant overall increase not credibly attributable to intervention, since the gradient before, though non-significant, is too similar to the gradient after intervention.

Statistical analysis title	HCRP Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04 [18]
Method	Mixed models analysis

Notes:

[18] - Significant overall increase not credibly attributable to intervention, since the gradient before, though non-significant, is too similar to the gradient after intervention

Statistical analysis title	HCRP Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.944 [19]
Method	Change in gradient

Notes:

[19] - Non significant

Secondary: Retroviral activity

End point title	Retroviral activity

End point description:

To date, there has been no definitive evidence to link HERVs as the cause of immune-mediated disease; however, HERV elements have been found in sera of people with a range of diseases such as type 1 diabetes, rheumatoid arthritis and SLE but not in control populations. The evidence suggesting a postulated link between HERVs and MS has been accumulating.
evidence is summarized to demonstrate that HERV-H and HERV-W are epidemiologically linked to patients with relapsing remitting MS. Further evidence was recently published by Perron et al. (4) that also links MS to a HERV which Perron calls multiple sclerosis associated retroviral element (MSRV). Raltegravir effect in relation to MS is not known, it may act by inhibiting HERVs, possibly in a similar mode of action that Raltegravir inhibits HIV replication.

End point type	Secondary

End point timeframe:

Changes in mean after - before

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20[20]		
Units: Changes in mean after - before/ dim-less				
arithmetic mean (standard deviation)				
MSRV_a	-0.01 (± 0.06)	-0.01 (± 0.06)		
MSRV_b	-0.01 (± 0.08)	-0.01 (± 0.08)		
HERV_c	0 (± 0.09)	0 (± 0.09)		
HERV_d	0 (± 0.07)	0 (± 0.07)		
HERV_e	0.01 (± 0.09)	0.01 (± 0.09)		
HERV_f	0.01 (± 0.04)	0.01 (± 0.04)		
HERV_W_a	-0.05 (± 0.07)	-0.05 (± 0.07)		
HERV_H_b	0.03 (± 0.13)	0.03 (± 0.13)		
HERV_H_c	0.03 (± 0.1)	0.03 (± 0.1)		
HERV_H_d	0.05 (± 0.14)	0.05 (± 0.14)		
HERV_W_e	0 (± 0.09)	0 (± 0.09)		
HERV_W_f	0.02 (± 0.19)	0.02 (± 0.19)		
PROP_B_g	0.46 (± 1.37)	0.46 (± 1.37)		
PROP_mon_h	-1.98 (± 4.31)	-1.98 (± 4.31)		
HERV_W_i	-0.01 (± 0.06)	-0.01 (± 0.06)		
HERV_H_j	0.12 (± 0.05)	0.12 (± 0.05)		
HERV_H_k	0.03 (± 0.09)	0.03 (± 0.09)		
HERV_H_l	0.02 (± 0.14)	0.02 (± 0.14)		
HERV_W_m	-0.03 (± 0.06)	-0.03 (± 0.06)		
HERV_W_n	0.04 (± 0.12)	0.04 (± 0.12)		

Notes:

[20] - HERV_W_a; HERV_W_m; HERV_W_n n=18
HERV_H_b; HERV_H_c; HERV_H_k n=17
HERV_W_i n=13
HERV_H_j n=15

Statistical analyses

Statistical analysis title	One sample t-test MSRV_a

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.551 [21]
Method	One sample t-test

Notes:

[21] - Non significant.

Statistical analysis title	One sample t-test MSRV_b

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.484 [22]
Method	One sample t-test

Notes:

[22] - Non significant.

Statistical analysis title	One sample t-test HERV_c

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.835 [23]
Method	One sample t-test

Notes:

[23] - Non significant.

Statistical analysis title	One sample t-test HERV_d

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.928
Method	One sample t-test

Statistical analysis title	One sample t-test HERV_e

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.563 [24]
Method	One sample t-test

Notes:

[24] - Non significant.

Statistical analysis title	One sample t-test HERV_f

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing

whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.408 [25]
Method	One sample t-test

Notes:

[25] - Non significant.

Statistical analysis title	One sample t-test HERV_W_a

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.012 [26]
Method	One sample t-test

Notes:

[26] - There is a significant drop in mean from before to after; however, there is a negative gradient of decline throughout the trial period. Therefore the after vs before drop cannot reasonably be attributed to the intervention.

Statistical analysis title	One sample t-test HERV_H_b

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.372 [27]
Method	One sample t-test

Notes:

[27] - Non significant.

Statistical analysis title	One sample t-test HERV_H_c

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.177 [28]
Method	One sample t-test

Notes:

[28] - Non significant.

Statistical analysis title	One sample t-test HERV_H_d

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.113 [29]
Method	One sample t-test

Notes:

[29] - Non significant.

Statistical analysis title	One sample t-test HERV_W_e

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.907 [30]
Method	One sample t-test

Notes:

[30] - Non significant.

Statistical analysis title	One sample t-test HERV_W_f

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.632 [31]
Method	One sample t-test

Notes:

[31] - Non significant.

Statistical analysis title	One sample t-test PROP_B_g

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.148 [32]
Method	One sample t-test

Notes:

[32] - Non significant.

Statistical analysis title	One sample t-test PROP_mon_h

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.053
Method	One sample t-test

Statistical analysis title	One sample t-test HERV_W_i

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.561 [33]
Method	One sample t-test

Notes:

[33] - Non significant.

Statistical analysis title	One sample t-test HERV_H_j

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.029 [34]
Method	One sample t-test

Notes:

[34] - Non significant.

Statistical analysis title	One sample t-test HERV_H_k

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.266 [35]
Method	One sample t-test

Notes:

[35] - Non significant.

Statistical analysis title	One sample t-test HERV_H_l

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.522 [36]
Method	One sample t-test

Notes:

[36] - Non significant.

Statistical analysis title	One sample t-test HERV_W_m

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.035 [37]
Method	One sample t-test

Notes:

[37] - Non significant.

Statistical analysis title	One sample t-test HERV_W_n

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.158 [38]
Method	One sample t-test

Notes:

[38] - Non significant.

Statistical analysis title	Mixed model MSRV_a

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear

mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.364 [39]
Method	Mixed models analysis

Notes:

[39] - Non significant.

Statistical analysis title	Mixed model MSRV_b

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.433 [40]
Method	Mixed models analysis

Notes:

[40] - Non significant.

Statistical analysis title	Mixed model HERV_c

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.775 [41]
Method	Mixed models analysis

Notes:

[41] - Non significant.

Statistical analysis title	Mixed model HERV_d

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.609 [42]
Method	Mixed models analysis

Notes:

[42] - Non significant.

Statistical analysis title	Mixed model HERV_e

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.781 [43]
Method	Mixed models analysis

Notes:

[43] - Non significant.

Statistical analysis title	Mixed model HERV_f

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.324 [44]
Method	Mixed models analysis

Notes:

[44] - Non significant.

Statistical analysis title	Mixed model HERV_W_a

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	Mixed models analysis

Statistical analysis title	Mixed model HERV_H_b

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.307 [45]
Method	Mixed models analysis

Notes:

[45] - Non significant.

Statistical analysis title	Mixed model HERV_H_c

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.212 [46]
Method	Mixed models analysis

Notes:

[46] - Non significant.

Statistical analysis title	Mixed model HERV_H_d

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.203 [47]
Method	Mixed models analysis

Notes:

[47] - Non significant.

Statistical analysis title	Mixed model HERV_W_e

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.235 [48]
Method	Change in gradient

Notes:

[48] - Non significant.

Statistical analysis title	Mixed model HERV_W_f

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.627 [49]
Method	Mixed models analysis

Notes:

[49] - Non significant.

Statistical analysis title	Mixed model PROP_B_g

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.298 [50]
Method	Mixed models analysis

Notes:

[50] - Non significant.

Statistical analysis title	Mixed model PROP_mon_h

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.16 [51]
Method	Mixed models analysis

Notes:

[51] - Non significant.

Statistical analysis title	Mixed model HERV_W_i

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.93 [52]
Method	Mixed models analysis

Notes:

[52] - Non significant.

Statistical analysis title	Mixed model HERV_H_j

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	Mixed models analysis

Statistical analysis title	Mixed model HERV_H_k

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient’s values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.642
Method	Mixed models analysis

Statistical analysis title	Mixed model HERV_H_l

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient’s values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.807
Method	Mixed models analysis

Statistical analysis title	Mixed model HERV_W_m

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient’s values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Mixed models analysis

Statistical analysis title	Mixed model HERV_W_n

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear

mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.259 [53]
Method	Mixed models analysis

Notes:

[53] - Non significant.

Statistical analysis title	Change in gradient MSRV_a

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.488 [54]
Method	Change in gradient

Notes:

[54] - Non significant.

Statistical analysis title	Change in gradient MSRV_b

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.691 [55]
Method	Change in gradient

Notes:

[55] - Non significant.

Statistical analysis title	Change in gradient HERV_c

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.172 [56]
Method	Mixed models analysis

Notes:

[56] - Non significant.

Statistical analysis title	Change in gradient HERV_d

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.802 [57]
Method	Change in gradient

Notes:

[57] - Non significant.

Statistical analysis title	Change in gradient HERV_e

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.621 [58]
Method	Change in gradient

Notes:

[58] - Non significant.

Statistical analysis title	Change in gradient HERV_f

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.533 [59]
Method	Change in gradient

Notes:

[59] - Non significant.

Statistical analysis title	Change in gradient HERV_W_a

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.438 [60]
Method	Change in gradient

Notes:

[60] - Non significant.

Statistical analysis title	Change in gradient HERV_H_b

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.012 [61]
Method	Mixed models analysis

Notes:

[61] - Gradient change significant P=0.012. Gradient before borderline significantly negative. After is significantly positive. Decline in values in period before intervention appears to change significantly after v 5 into an increase in values over time.

Statistical analysis title	Change in gradient HERV_H_c

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.197 [62]
Method	Mixed models analysis

Notes:

[62] - Non significant.

Statistical analysis title	Change in gradient HERV_H_d

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over

the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01 [63]
Method	Mixed models analysis

Notes:

[63] - Borderline significant negative gradient before changes to significant positive after v 5. Decline in values appears to change significantly after intervention into increase in values over time.

Statistical analysis title	Change in gradient HERV_W_e

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008 [64]
Method	Change in gradient

Notes:

[64] - Significantly negative decline before visit 5 changes to a non-significant positive gradient after; the change in gradients is significant P=0.008.

Statistical analysis title	Change in gradient HERV_W_f

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.195 [65]
Method	Change in gradient

Notes:

[65] - Non significant.

Statistical analysis title	Change in gradient PROP_B_g

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.405 [66]
Method	Change in gradient

Notes:

[66] - Non significant.

Statistical analysis title	Change in gradient PROP_mon_h

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.072 [67]
Method	Change in gradient

Notes:

[67] - Non-significant positive gradient changes to borderline significant negative gradient; change in gradient borderline significant consistent with intervention effect. Interpretation dependent on biological plausibility due to possibility Type 1 error

Statistical analysis title	Change in gradient HERV_W_i

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.552 [68]
Method	Change in gradient

Notes:

[68] - Non-significant.

Statistical analysis title	Change in gradient HERV_H_i

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.054 [69]
Method	Change in gradient

Notes:

[69] - A non-signifiant negative gradient before intervention changes to a significantly positive gradient after; the change is borderline signififcant P=0.054.

Statistical analysis title	Change in gradient HERV_H_k

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.802 [70]
Method	Change in gradient

Notes:

[70] - Non-significant.

Statistical analysis title	Change in gradient HERV_H_l

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.314 [71]
Method	Change in gradient

Notes:

[71] - Non-significant.

Statistical analysis title	Change in gradient HERV_W_m

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.178 [72]
Method	Change in gradient

Notes:

[72] - Non-significant.

Statistical analysis title	Change in gradient HERV_W_n

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient

of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.047 [73]
Method	Change in gradient

Notes:

[73] - Non-significant decline before visit 5 becomes a borderline significant increase after; the change in gradient is significant. Biological plausibility important, both for change displayed and for negative correlation with Gd T1 lesions.

Secondary: EDSS Clinical responses (disability data)

End point title	EDSS Clinical responses (disability data)

End point description:

Expanded Disability Status Scale score at screening between 0-6.0 inclusive for trial eligibility. Disability measures summaries at baseline, before and after.

End point type	Secondary

End point timeframe:

EDSS performed at visits 1, 2, 4, 6 and 8. Summaries of disability measured at baseline, before and after.

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Within patient change in means				
arithmetic mean (standard deviation)				
EDSS	0.14 (± 0.45)	0.14 (± 0.45)		

Statistical analyses

Statistical analysis title	One-sample t-test
Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.179
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[74] - One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Statistical analysis title	Mixed model
Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	= 0.13
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[75] - Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Secondary: MSFC Clinical responses (disability data)

End point title	MSFC Clinical responses (disability data)

End point description:

MSFC (the standardly derived composite score from 9-hole peg test (9HPT), timed walk and PASAT scores); higher scores indicate less disability

End point type	Secondary

End point timeframe:

Changes in mean after - before (treatment)

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Changes in mean after - before				
arithmetic mean (standard deviation)				
MSFC	0.23 (± 0.28)	0.23 (± 0.28)		

Statistical analyses

Statistical analysis title	One-sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [76]
Method	One sample t-test

Notes:

[76] - Both change and change in gradient significant.

Statistical analysis title	Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [77]
Method	Mixed models analysis

Notes:

[77] - Both change and change in gradient significant.

Secondary: 9HPT speed Clinical responses (disability data)

End point title	9HPT speed Clinical responses (disability data)

End point description:

End point type	Secondary

End point timeframe:

Changes in mean after - before

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Changes in mean after - before				
arithmetic mean (standard deviation)				
9HPT	0.003 (± 0.003)	0.003 (± 0.003)		

Statistical analyses

Statistical analysis title	One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [78]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[78] - Highly significant improvement.
There are statistically significant improvements in the 9HPT, but the rate of improvement slowed after intervention. This is not consistent with an effect of intervention.

Statistical analysis title	Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [79]
Method	Mixed models analysis

Notes:

[79] - There are statistically significant improvements in the 9HPT, but the rate of improvement slowed after intervention. This is not consistent with an effect of intervention.

Statistical analysis title	Change in gradient
Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217 [80]
Method	Mixed models analysis

Notes:

[80] - No significant gradient change. Rate of improvement substantially greater before than after intervention

Secondary: 25 foot walk speed Clinical responses (disability data)

End point title	25 foot walk speed Clinical responses (disability data)

End point description:

End point type	Secondary

End point timeframe:

Changes in mean after - before

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Changes in mean after - before				
arithmetic mean (standard deviation)				
25' walk speed	-0.04 (± 0.47)	-0.04 (± 0.47)		

Statistical analyses

Statistical analysis title	One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.738 [81]
Method	One sample t-test

Notes:

[81] - Non significant.

Statistical analysis title	Mixed model analysis

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.669 [82]
Method	Mixed models analysis

Notes:

[82] - Non significant.

Statistical analysis title	Change in gradient

Statistical analysis description:

Change in gradient': this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.908 [83]
Method	change in gradient

Notes:

[83] - Non significant

Secondary: PASAT Clinical responses (disability data)

End point title	PASAT Clinical responses (disability data)

End point description:

End point type	Secondary

End point timeframe:

Changes in mean after - before

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Changes in mean after - before				
arithmetic mean (standard deviation)				
PASAT	4.66 (± 5.21)	4.66 (± 5.21)		

Statistical analyses

Statistical analysis title	One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [84]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[84] - Highly significant improvement, but rate of improvement substantially greater before than after intervention

Statistical analysis title	Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [85]
Method	Mixed models analysis

Notes:

[85] - Highly significant improvement, but rate of improvement substantially greater before than after intervention.

Statistical analysis title	Change in gradient

Statistical analysis description:

Change in gradient': this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [86]
Method	Change in gradient
Parameter estimate	Slope
Confidence interval	
sides	2-sided

Notes:

[86] - There is a significant gradient change, but rate of improvement substantially greater before than after intervention

Secondary: Quality of life measures

End point title	Quality of life measures

End point description:

Quality of life measures: patient reported outcomes (PROs) including 3 questionnaires: Health Status Questionnaire (SF-36), Multiple Sclerosis Impact Scale (MSIS-29), Multiple Sclerosis Walking Scale (MSWS-12) and 2 Visual Analogue Scales (VAS): Patient Fatigue Assessment (PFA) and Patient Pain Assessment (PPA). The SF-36 generates 8 subscale scores for Physical Functional Scale (PF), Role-Physical Scale (RP), Bodily Pain Scale (BP), General Health scale (GH), Vitality Scale (VT), Social Functioning Scale (SF), Role Emotional Scale (RE) and Mental Health Scale (MH). Higher scores indicate better health/quality of life on all eight SF-36 measures, and worse health/quality of life on the last four measures.

End point type	Secondary

End point timeframe:

Quality of life measures baseline, before and after summeries. Patient reported outcomes completed at visits 2 (baseline), 3, 4 and 5 (before) and 6, 7 and 8 (after).

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: Change after - before				
arithmetic mean (standard deviation)				
SF36 PF Before	72.63 (± 23.37)	72.63 (± 23.37)		
Sf36 PF After	71.71 (± 26.04)	71.71 (± 26.04)		
SF36 RP Before	59.06 (± 39.66)	59.06 (± 39.66)		
Sf36 RP After	49.58 (± 38.47)	49.58 (± 38.47)		
Sf36 BP Before	72.22 (± 19.59)	72.22 (± 19.59)		
SF36 BP After	66.8 (± 22.63)	66.8 (± 22.63)		
SF36 GH Before	50.86 (± 15.02)	50.86 (± 15.02)		
SF36 GH After	46.18 (± 16.86)	46.18 (± 16.86)		
SF36 VT Before	42.98 (± 21.53)	42.98 (± 21.53)		
SF36 VT After	48.04 (± 22.21)	48.04 (± 22.21)		
SF36 Sf After	77.92 (± 16.06)	77.92 (± 16.06)		

SF36 RE Before	71.92 (± 33.39)	71.92 (± 33.39)		
SF36 RE After	63.3 (± 38.35)	63.3 (± 38.35)		
SF36 MH Before	65.85 (± 12.77)	65.85 (± 12.77)		
SF36 MH After	71.57 (± 11.05)	71.57 (± 11.05)		
PFA Before	40.02 (± 24.36)	40.02 (± 24.36)		
PFA After	38.51 (± 26.35)	38.51 (± 26.35)		
PPA Before	22.8 (± 19.46)	22.8 (± 19.46)		
PPA After	27.96 (± 21.46)	27.96 (± 21.46)		
MSIS Before	52.16 (± 17.4)	52.16 (± 17.4)		
MSIS After	50.06 (± 13.95)	50.06 (± 13.95)		
MSWS-12 Before	20.87 (± 9.61)	20.87 (± 9.61)		
MSWS-12 After	20.52 (± 9.76)	20.52 (± 9.76)		

Statistical analyses

Statistical analysis title	SF36 PF One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.713 [87]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[87] - Non significant

Statistical analysis title	SF36 PF Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.685 [88]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[88] - Non significant

Statistical analysis title	SF36 PF Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.063 [89]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[89] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 RP One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.198 [90]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[90] - Non significant.

Statistical analysis title	SF36 RP Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.034 [91]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[91] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 RP Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.873 [92]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[92] - Non significant.

Statistical analysis title	SF36 BP One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.14 [93]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[93] - Non significant

Statistical analysis title	SF36 BP Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.024 [94]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[94] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 BP Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.026 [95]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[95] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 GH One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.019 [96]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[96] - Significant improvements in well-being/slowing of deterioration after compared to before intervention. Although consistent with effect of raltegravir, this is most credibly attributable to placebo effect of patients receiving unblinded intervention.

Statistical analysis title	SF36 GH Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001 [97]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[97] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 GH Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.022 [98]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[98] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 VT One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.14 [99]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[99] - Non significant.

Statistical analysis title	SF36 VT Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011 [100]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[100] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 VT Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 [101]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[101] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 SF One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.567 [102]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[102] - Non significant.

Statistical analysis title	SF36 SF Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.414 [103]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[103] - Non significant.

Statistical analysis title	SF36 SF Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.039 [104]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[104] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	SF36 RE One sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.252 [105]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[105] - Non significant.

Statistical analysis title	SF36 RE Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.096 [106]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[106] - Non significant.

Statistical analysis title	SF36 RE Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.768 [107]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[107] - Non significant.

Statistical analysis title	PFA One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.665 [108]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[108] - Non significant.

Statistical analysis title	PFA Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.683 [109]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[109] - Non significant.

Statistical analysis title	PFA Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.057 [110]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[110] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	PPA One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.17 [111]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[111] - Non significant.

Statistical analysis title	PPA Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.144 [112]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[112] - Non significant.

Statistical analysis title	PPA Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01 [113]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[113] - Statistically significant improvements in the period after compared to before intervention. Although consistent with an effect of raltegravir, this is most credibly attributable to the placebo effect of patients receiving an unblinded intervention.

Statistical analysis title	MSIS One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.477 [114]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[114] - Non significant.

Statistical analysis title	MSIS Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.22 [115]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[115] - Non significant.

Statistical analysis title	MSIS Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.196 [116]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[116] - Non significant.

Statistical analysis title	MSWS One sample t-test

Statistical analysis description:

One-sample t-test': this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.817 [117]
Method	One sample t-test
Parameter estimate	Mean difference (net)

Notes:

[117] - Non significant.

Statistical analysis title	MSWS Mixed model

Statistical analysis description:

Mixed model': this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.772 [118]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Notes:

[118] - Non significant.

Statistical analysis title	MSWS Change in gradient

Statistical analysis description:

Change in gradient: this uses the linear mixed model, using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of

change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.12 [119]
Method	Change in gradient
Parameter estimate	Slope

Notes:

[119] - Non significant.

Secondary: EBV copy number in saliva

End point title	EBV copy number in saliva

End point description:

Epstein–Barr virus (EBV), also called human herpesvirus 4 (HHV-4), infection is associated with with a higher risk of certain autoimmune diseases, such as Multiple Sclerosis. In particular, people who have had glandular fever, the symptomatic EBV infection , have a higher risk to develop MS.
EBV may be found in the saliva of someone who has had glandular fever for several months after their symptoms pass, and most people may continue to have the virus in their saliva on and off for years. Studies of dynamics of virus shedding in healthy carriers demonstrate that EBV shedding into saliva is constant.

End point type	Secondary

End point timeframe:

Changes in mean after - before.

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	13		
Units: Copies/microlitre				
arithmetic mean (standard deviation)				
EBV	-16.3 (± 46.02)	-16.3 (± 46.02)		

Statistical analyses

Statistical analysis title	EBV one sample t-test

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.226 [120]
Method	One sample t-test

Notes:

[120] - Non significant.

Statistical analysis title	EBV Mixed model

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 2 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.616 [121]
Method	Mixed models analysis

Notes:

[121] - Non significant.

Statistical analysis title	EBV change in gradient
Comparison groups	Treatment v ITT
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.219 [122]
Method	Change in gradient

Notes:

[122] - Non significant.

Secondary: Laboratory safety data

End point title	Laboratory safety data

End point description:

Laboratory safety outcomes. Assessments collected at screening were used to determe study eligibility only. Safety assessments were collected at all visits.
Severity of abnormal results was evaluated by the investigator as mild, moderate or severe. Lab findings which the investigator felt were clinically significant based on the Laboratory Guidelines were recorded as adverse events. The relationship of the adverse event to the administration of the study drug was also determined by the investigator.

End point type	Secondary

End point timeframe:

Changes in after - before (treatment).

End point values	Treatment	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: After - before changes in mean				
arithmetic mean (standard deviation)				
Adjusted calcium serum	0.02 (± 0.05)	0.02 (± 0.05)		
ALT	1.12 (± 8.75)	1.12 (± 8.75)		
AST	1.24 (± 4.83)	1.24 (± 4.83)		
Basophil count	0 (± 0.02)	0 (± 0.02)		

Chloride serum	-0.75 (± 1.65)	-0.75 (± 1.65)		
Cholesterol HDL ratio serum	0.04 (± 0.21)	0.04 (± 0.21)		
Cholesterol serum	0.28 (± 0.38)	0.28 (± 0.38)		
Creatinine serum	2.08 (± 5.91)	2.08 (± 5.91)		
Eosinophil count	0 (± 0.06)	0 (± 0.06)		
Estimated GFR	-3 (± 9.77)	-3 (± 9.77)		
GGT	-0.5 (± 8.18)	-0.5 (± 8.18)		
Glucose plasma	-0.18 (± 0.47)	-0.18 (± 0.47)		
Haemoglobin	-0.13 (± 0.56)	-0.13 (± 0.56)		
HDL cholesterol serum	0.05 (± 0.16)	0.05 (± 0.16)		
LDL Cholesterol serum	0.17 (± 0.32)	0.17 (± 0.32)		
Lymphocyte count	0.05 (± 0.31)	0.05 (± 0.31)		
Monocyte count	0 (± 0.11)	0 (± 0.11)		
Neutrophil count	0.15 (± 0.61)	0.15 (± 0.61)		
Platelet count	6.86 (± 13.92)	6.86 (± 13.92)		
Potassium serum	0.05 (± 0.15)	0.05 (± 0.15)		
Sodium serum	0.14 (± 1.57)	0.14 (± 1.57)		
Total bilirubin serum	0.18 (± 1.5)	0.18 (± 1.5)		
Triglicerides serum	0.08 (± 0.29)	0.08 (± 0.29)		
Urea serum	0.24 (± 0.78)	0.24 (± 0.78)		
White blood count	0.22 (± 0.71)	0.22 (± 0.71)		

Statistical analyses

Statistical analysis title	One sample t-test Adjusted Calcium serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.025 [123]
Method	One sample t-test

Notes:

[123] - There was a significant increase after vs before, 0.02 (P=0.025). However, there was no significant change in gradient P=0.406

Statistical analysis title	One sample t-test ALT

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.575 [124]
Method	One sample t-test

Notes:

[124] - Non significant.

Statistical analysis title	One sample t-test AST

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.266 [125]
Method	One sample t-test

Notes:

[125] - Non significant.

Statistical analysis title	One sample t-test basophil count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.883 [126]
Method	One sample t-test

Notes:

[126] - Non significant.

Statistical analysis title	One sample t-test chloride serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.055 [127]
Method	One sample t-test

Notes:

[127] - Borderline significant drop, -0.75 (P=0.055). However, there was no significant change in gradient, P=0.194.

Statistical analysis title	One sample t-test Cholesterol HDL ratio serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.369 [128]
Method	One sample t-test

Notes:

[128] - Non significant.

Statistical analysis title	One sample t-test Cholesterol serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 [129]
Method	One sample t-test

Notes:

[129] - There was a significant increase P=0.004. However, there was no significant change in gradient P=0.437. Faster increase before than after.

Statistical analysis title	One sample t-test Creatinine serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.132 [130]
Method	One sample t-test

Notes:

[130] - Non significant.

Statistical analysis title	One sample t-test Eosinophil count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.855 [131]
Method	One sample t-test

Notes:

[131] - Non significant.

Statistical analysis title	One sample t-test Estimated GFR

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing

whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.186 [132]
Method	One sample t-test

Notes:

[132] - Non significant.

Statistical analysis title	One sample t-test GGT

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.789 [133]
Method	One sample t-test

Notes:

[133] - Non significant.

Statistical analysis title	One sample t-test Glucose plasma

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.108 [134]
Method	One sample t-test

Notes:

[134] - Non significant.

Statistical analysis title	One sample t-test Haemoglobin

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.308 [135]
Method	One sample t-test

Notes:

[135] - Non significant.

Statistical analysis title	One sample t-test HDL Cholesterol serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.174 [136]
Method	One sample t-test

Notes:

[136] - Non significant.

Statistical analysis title	One sample t-test LDL Cholesterol serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.027 [137]
Method	One sample t-test

Notes:

[137] - There was a significant increase, but no significant change in gradient P=0.432.

Statistical analysis title	One sample t-test Lymphocyte count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.465 [138]
Method	One sample t-test

Notes:

[138] - Non significant.

Statistical analysis title	One sample t-test Monocyte count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.958 [139]
Method	One sample t-test

Notes:

[139] - Non significant.

Statistical analysis title	One sample t-test Neutrophil count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.291 [140]
Method	One sample t-test

Notes:

[140] - Non significant.

Statistical analysis title	One sample t-test Platelet count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.04 [141]
Method	One sample t-test

Notes:

[141] - There was asignificant increase P=0.040. However, there was no significant change in gradient P=0.352.

Statistical analysis title	One sample t-test Potassium serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.161 [142]
Method	One sample t-test

Notes:

[142] - There was asignificant increase P=0.040. However, there was no significant change in gradient P=0.352.

Statistical analysis title	One sample t-test Sodium serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.692 [143]
Method	One sample t-test

Notes:

[143] - Non significant.

Statistical analysis title	One sample t-test Total bilirubin serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.591 [144]
Method	One sample t-test

Notes:

[144] - Non significant.

Statistical analysis title	One sample t-test Triglicerides serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.225 [145]
Method	One sample t-test

Notes:

[145] - Non significant.

Statistical analysis title	One sample t-test Urea serum

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.183 [146]
Method	One sample t-test

Notes:

[146] - Non significant.

Statistical analysis title	One sample t-test White blood count

Statistical analysis description:

One-sample t-test: this uses one datapoint per patient, the within-patient change in means, testing whether the mean of these changes is significant.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.184 [147]
Method	One sample t-test

Notes:

[147] - Non significant.

Statistical analysis title	Mixed model Adjusted calcium serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.027 [148]
Method	Mixed models analysis

Notes:

[148] - There was a significant increase after vs before. However, there was no significant change in gradient.

Statistical analysis title	Mixed model ALT

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.643 [149]
Method	Mixed models analysis

Notes:

[149] - Non significant.

Statistical analysis title	Mixed model AST

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.265 [150]
Method	Mixed models analysis

Notes:

[150] - Non significant.

Statistical analysis title	Mixed model Basophil count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear

mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.954 [151]
Method	Mixed models analysis

Notes:

[151] - Non significant.

Statistical analysis title	Mixed model Chloride serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.032 [152]
Method	Mixed models analysis

Notes:

[152] - Borderline significant drop. However, there was no significant change in gradient

Statistical analysis title	Mixed model Cholesterol HDL ratio serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.441 [153]
Method	Mixed models analysis

Notes:

[153] - Borderline significant drop.

Statistical analysis title	Mixed model Cholesterol serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0 [154]
Method	Mixed models analysis

Notes:

[154] - There was a significant increase. However, there was no significant change in gradient.

Statistical analysis title	Mixed model Creatinine serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.097 [155]
Method	Mixed models analysis

Notes:

[155] - Non significant.

Statistical analysis title	Mixed model Eosinophil count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.711 [156]
Method	Mixed models analysis

Notes:

[156] - Non significant.

Statistical analysis title	Mixed model Estimated GFR

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.153 [157]
Method	Mixed models analysis

Notes:

[157] - Non significant.

Statistical analysis title	Mixed model GGT

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.794 [158]
Method	Mixed models analysis

Notes:

[158] - Non significant.

Statistical analysis title	Mixed model Glucose Plasma

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.196 [159]
Method	Mixed models analysis

Notes:

[159] - Non significant.

Statistical analysis title	Mixed model Haemoglobin

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.168 [160]
Method	Mixed models analysis

Notes:

[160] - Non significant.

Statistical analysis title	Mixed model HDL cholesterol serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.101 [161]
Method	Mixed models analysis

Notes:

[161] - Non significant.

Statistical analysis title	Mixed model LDL cholesterol serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018 [162]
Method	Mixed models analysis

Notes:

[162] - There was a significant increase. However, there was no significant change in gradient.

Statistical analysis title	Mixed model Lymphocyte count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.304 [163]
Method	Mixed models analysis

Notes:

[163] - Non significant.

Statistical analysis title	Mixed model Monocyte count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.789 [164]
Method	Mixed models analysis

Notes:

[164] - Non significant.

Statistical analysis title	Mixed model Neutrophil count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.244 [165]
Method	Mixed models analysis

Notes:

[165] - Non significant.

Statistical analysis title	Mixed model Platelet count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.013 [166]
Method	Mixed models analysis

Notes:

[166] - There was a significant increase. However, there was no significant change in gradient.

Statistical analysis title	Mixed model Potassium serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.143 [167]
Method	Mixed models analysis

Notes:

[167] - Non significant.

Statistical analysis title	Mixed model Sodium serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.732 [168]
Method	Mixed models analysis

Notes:

[168] - Non significant.

Statistical analysis title	Mixed model Total bilirubin serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.57 [169]
Method	Mixed models analysis

Notes:

[169] - Non significant.

Statistical analysis title	Mixed model Triglicerides serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear

mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.133 [170]
Method	Mixed models analysis

Notes:

[170] - Non significant.

Statistical analysis title	Mixed model Urea serum

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.107 [171]
Method	Mixed models analysis

Notes:

[171] - Non significant.

Statistical analysis title	Mixed model White blood count

Statistical analysis description:

Mixed model: this compares the change in means in a potentially more powerful analysis using a linear mixed model which uses all of a patient's values, from visit 1 to visit 8.

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.154 [172]
Method	Mixed models analysis

Notes:

[172] - Non significant.

Statistical analysis title	Change in gradient Adjusted calcium serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.406 [173]
Method	Change in gradient

Notes:

[173] - No significant chnge

	gradient	SE	z	P-value	95% Conf. Int	
before	-.0000267	.005385	-0.00	0.996	-.0105811	.0105277

after .0077586 .0053828 1.44 0.149 -.0027916 .0183087

Statistical analysis title	Change in gradient ALT

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.179 [174]
Method	Change in gradient

Notes:

[174] - No signif change

	gradient	SE	z	P-value	95% Conf. Int
before	-.0000267	.005385	-0.00	0.996	-.0105811 .0105277
after	.0077586	.0053828	1.44	0.149	-.0027916 .0183087

Statistical analysis title	Change in gradient AST

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.385 [175]
Method	Change in gradient

Notes:

[175] - Non significant.

Statistical analysis title	Change in gradient Basophil count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.779 [176]
Method	Change in gradient

Notes:

[176] - Non significant.

Statistical analysis title	Change in gradient Chloride serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.194 [177]
Method	Change in gradient

Notes:

[177] - No signif change

	gradient	SE	z	P-value	95% Conf. Int	
before	.1363255	.2036459	0.67	0.503	-.2628131	.5354641
after	-.3119152	.1915487	-1.63	0.103	-.6873437	.0635134

Statistical analysis title	Change in gradient Chlolesterol HDL ratio serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.928 [178]
Method	Change in gradient

Notes:

[178] - Non significant.

Statistical analysis title	Change in gradient Chlolesterol serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.437 [179]
Method	Change in gradient

Notes:

[179] - No signif change

	gradient	SE	z	P-value	95% Conf. Int	
before	.0826927	.043773	1.89	0.059	-.0031008	.1684862
after	.0258226	.040227	0.64	0.521	-.0530208	.1046661

Statistical analysis title	Change in gradient Creatinine serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.769 [180]
Method	Change in gradient

Notes:

[180] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Eosinophil count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.768 [181]
Method	Change in gradient

Notes:

[181] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Estimated GFR

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.874 [182]
Method	Change in gradient

Notes:

[182] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Estimated GGT

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.345 [183]
Method	Change in gradient

Notes:

[183] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Estimated Glucose plasma

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.072 [184]
Method	Change in gradient

Notes:

[184] - There was a borderline significant gradient change P=0.072, from a non-significant increase before to a significant decline after.

Statistical analysis title	Change in gradient Haemoglobin

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.558 [185]
Method	Change in gradient

Notes:

[185] - There was no significant change in gradient.

Statistical analysis title	Change in gradient HDL Cholesterol serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.843 [186]
Method	Change in gradient

Notes:

[186] - There was no significant change in gradient.

Statistical analysis title	Change in gradient LDL Cholesterol serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient

of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.432 [187]
Method	Change in gradient

Notes:

[187] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Lymphocyte count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.775 [188]
Method	Change in gradient

Notes:

[188] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Monocyte count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.089 [189]
Method	Change in gradient

Notes:

[189] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Neutrophil count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.899 [190]
Method	Change in gradient

Notes:

[190] - There was no significant change in gradient.

Statistical analysis title	Change in gradient Platelet count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.352 [191]
Method	Change in gradient

Notes:

[191] - No signif change

	gradient	SE	z	P-value	95% Conf. Int	
before	-.274596	1.820794	-0.15	0.880	-3.843288	3.294096
after	2.592704	1.709353	1.52	0.129	-.7575659	5.942974

Statistical analysis title	Change in gradient Potassium serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.221 [192]
Method	Change in gradient

Notes:

[192] - There was no significant change in gradient

Statistical analysis title	Change in gradient Sodium serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.445 [193]
Method	Change in gradient

Notes:

[193] - There was no significant change in gradient

Statistical analysis title	Change in gradient total bilirubin serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.123 [194]
Method	Change in gradient

Notes:

[194] - There was no significant change in gradient

Statistical analysis title	Change in gradient Triglicerides serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.767 [195]
Method	Change in gradient

Notes:

[195] - There was no significant change in gradient

Statistical analysis title	Change in gradient Urea serum

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.197 [196]
Method	Change in gradient

Notes:

[196] - There was no significant change in gradient

Statistical analysis title	Change in gradient White blood count

Statistical analysis description:

Change in gradient: this uses the linear mixed model, again using all of a patient's measurements over the seven visits, to determine if the gradient of change after is significantly different from the gradient of change before. Note that the p-value refers to the change in gradients, not to either of the two gradients, which may or may not be significant (ie significantly different from zero).

Comparison groups	Treatment v ITT
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.674 [197]
Method	Change in gradient

Notes:

[197] - There was no significant change in gradient

Secondary: Adverse events

End point title	Adverse events

End point description:

End point type	Secondary

End point timeframe:

After - before (treatment) changes

End point values	Treatment	Per protocol	ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	16	20	
Units: Number of visits with adverse events				
arithmetic mean (standard deviation)				
Number of visits with AEs before intervention	2.35 (± 0.75)	2.31 (± 0.79)	2.35 (± 0.75)	
Number of visits with AEs after intervention	2.3 (± 0.73)	2.31 (± 0.79)	2.3 (± 0.73)	
Adverse events	-0.05 (± 1.28)	0 (± 1.37)	-0.05 (± 1.28)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information
Timeframe for reporting adverse events:
Reporting of adverse events from screening
Adverse event reporting additional description:
Adverse events were recorded for all subjects screened (n=31) and include events for patients who did not receive IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Non-serious adverse events

Reporting group description:

Adverse events were recorded from screening (n=31) and include subjects who did not receive IMP.

Serious adverse events	Non-serious adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
MS relapse	Additional description: MS relapse which required hospitalisation for administration of IV methylprednisolone. Normal practise would not have been to admit to hospital. However the patient had no care at home and could not care for self at home.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Non-serious adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
General disorders and administration site conditions			
Headache			

subjects affected / exposed	10 / 20 (50.00%)			
occurrences (all)	12			
Liver function test abnormal				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Liver function test increased				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Dizziness				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Fall				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	5			
Insomnia				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
poor sleep				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Swelling in left arm				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Stomach pain				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Loss of libido				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pyrexia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Dysphonia				

subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Problems concentrating				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Stiff neck				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Fainting				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Vivid dreams				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tiredness				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Night sweats				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Weight loss diet				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Lack of motivation				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Low blood pressure asymptomatic				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Chest pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Choking on liquids				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Flushing to face			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Strange sensation when swallowing			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Swelling in fingers			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Swelling feeling in fingers			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Immune system disorders			
Adenopathies			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Itchy eyes			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Allergic skin rash worsening			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hayfever congestion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hayfever worsening			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menopause onset			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Erectile dysfunction			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pelvic mass			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Wheeze			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Depression worsening			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Low mood			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Panic attack increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Emotional instability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Bruised knee (due to fall)			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Broken toenail			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cut knee			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Twisted knee			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hurt wrist			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac disorders			
Hypertension			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	7		
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Hypertension worsening			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Arrhythmia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Multiple sclerosis relapse			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	9		
Multiple sclerosis sensory relapse			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Sensory disturbance			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

Fatigue				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Fatigue increased				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Migraine				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Dysaesthesia worsening				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Nystagmus				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Neuropathic pain				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Tremor in hands				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Numbness - loss of sensation				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Tremor in arm worsened				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Subjective worsening of leg weakness				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Neurological signs worsening				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Back pain (burning sensation)				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Dyslipidemia			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	17		
Mycrocytic Anemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Normocytic anaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Visual fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Decreased vision			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Stye			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Defective gastro-ileal valve			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Bloated abdomen (during antibiotics)			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Itching subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3		
Eczema subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Fungal infection subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Fungal infection worsening subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Dry skin subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Petechial purpura subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Naevus subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Scar from mole removal subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Rash on face subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Mole on toe subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Allergic rash worsening subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Renal and urinary disorders Bladder dysfunction			

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Dysuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Bladder problems worsening			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	14 / 20 (70.00%)		
occurrences (all)	17		
Pain worsening			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Carpal tunnel syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cramps in legs			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Common cold			
subjects affected / exposed	14 / 20 (70.00%)		
occurrences (all)	21		
Urinary tract infection			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
Sore throat			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Sinusitis			

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Tooth infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Chest infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2013	Approved documents: • Protocol Version 5.0 • PIS/ICF Version 6.0 • Questionnaires Version 2.0 • Website Advertising Text Version 1.0 • Additional IMP Label 1. Updates to Patient Questionnaires The following questionnaires remain in the study and patients will be asked to complete these at visits 2-8. 1. Health Status Questionnaire (SF-36) 2. Multiple Sclerosis Impact Scale (MSIS-29) 3. Multiple Sclerosis Walking Scale (MSWS-12v2) The following assessments replace patient assessments of pain and fatigue. 1. Patient Fatigue Assessment – Visual Analogue Scale 2. Patient Pain Assessment – Visual Analogue Scale 2. Reduction of EDSS Frequency Frequency of EDSS assessments was reduced (every 2 months)as it was deemed unnecessary by the Chief Investigator to have this number of EDSS in the study. 3. Use of an Additional Pharmacy Label Additional IMP label to be attached to the study IMP. 4. Pregnancy Tests before MRI Clarification on pregnancy tests to be performed prior to MRI scans (standard of care but this information was not clearly outlined in the Protocol and Patient Information Sheet). 5. Advertising Materials In order to advertise the study on the websites of patient support groups such as the MS Society and Shift MS to aid recruitment.
11 November 2014	Approved document: Protocol Version 6.0 Summary of changes made to the protocol: 1. End of Trial Definition The end of study definition was revised from 'Last Patient Last Visit' to 'Last Patient Last Visit plus six months'. 2. Criteria for Premature Withdrawal Both protocol sections 3.4 and sections 5.8 of the protocol indicated the reasons for premature withdrawal from this study. However, section 3.4 did not include all reasons as given in protocol section 5.8. Section 3.4 was updated with the reason, which was previously present in protocol section 5.8 but missing in protocol section 3.4 : Severe or disabling MS relapse needing IVMP and admission to hospital during the 3 months on treatment phase of the study.

13 April 2015	Clarifications were made to the following sections of the protocol post last patient last visit: 1. Inclusion/Exclusion criteria section 3.3 2. Criteria for Premature Withdrawal section 3.4 3. Prior and concomitant therapies section 4.8 The amendment was approved by the MHRA but rejected by the ethics committee. Therefore it was felt appropriate to withdraw the amendment. MHRA were notified of this on 08/06/15.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: