Clinical trial results:
A randomized controlled clinical trial to determine if a combined screening /treatment programme can prevent premature failure of renal transplants due to chronic rejection in patients with HLA antibodies.

Summary

EudraCT number	2012-004308-36
Trial protocol	GB
Global end of trial date	29 November 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2023
First version publication date	12 March 2023
Summary attachment (see zip file)	CSR OUTSMART (Clinical Study Report v1.0_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	OuTSMART

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Anthony Dorling, Kings College London, 44 207188 5880 , anthony.dorling@kcl.ac.uk
Scientific contact	Anthony Dorling, Kings College London, 44 207188 5880 , anthony.dorling@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Anthony Dorling, Guy's and St Thomas' Foundation NHS Trust, 44 0207188 5880 , anthony.dorling@kcl.ac.uk
Scientific contact	Anthony Dorling, Guy's and St Thomas' Foundation NHS Trust, 44 0207188 5880 , anthony.dorling@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2020
Global end of trial reached?	Yes
Global end of trial date	29 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the time to graft failure in patients testing positive for HLA Ab at baseline or within 32 months of randomization who receive an optimized anti-rejection medication intervention with prednisone, Tac and MMF ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomization who remain on their established immunotherapy and whose clinicians are not aware of their Ab status.

Protection of trial subjects:

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, cure, administrative reasons or other reasons

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 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: 2037
Worldwide total number of subjects	2037
EEA total number of subjects	2037

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)	1767
From 65 to 84 years	270
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	2094[1]
Number of subjects completed	2037

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen fail: 57

Notes:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DSA BLC (B1)

Arm description:

Positive for Donor Specific Antibodies Biomarker Led Care

Arm type	Experimental
Investigational medicinal product name	Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Mycophenolate mofetil bd, tds or qds, or enteric coated mycophenolic acid bd, with daily dose determined according to local unit guidelines. The patient will be stabilized on the maximum tolerated dose.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus od or bd, according to local unit preference, with dose titrated to achieve 12-hour post-dose levels of 4g/L to 8g/L (4-8 ng/ml). The patient will be stabilized on the maximum tolerated dose that achieves these levels.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone od. Starting at 20mg for two weeks, then reducing by 5 mg od every two weeks down to their previous maintenance dose or 5mg od, if not previously taking.

Arm title	DSA SC (A1)

Arm description:

Positive Donor specific antibodies blinded standard care

Arm type	standard of care

No investigational medicinal product assigned in this arm

Arm title	Non-DSA BLC (B2)

Arm description:

Positive non- Donor specific antibodies Biomarker Led Care

Arm type	Experimental
Investigational medicinal product name	Mycophenolic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Mycophenolate mofetil bd, tds or qds, or enteric coated mycophenolic acid bd, with daily dose determined according to local unit guidelines. The patient will be stabilized on the maximum tolerated dose.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus od or bd, according to local unit preference, with dose titrated to achieve 12-hour post-dose levels of 4g/L to 8g/L (4-8 ng/ml). The patient will be stabilized on the maximum tolerated dose that achieves these levels.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone od. Starting at 20mg for two weeks, then reducing by 5 mg od every two weeks down to their previous maintenance dose or 5mg od, if not previously taking.

Arm title	Neg Unblinded (D)

Arm description:

HLA Ab negative unblinded standard of care

Arm type	standard of care

No investigational medicinal product assigned in this arm

Arm title	Neg Blinded (C)

Arm description:

HLA ab negative blinded standard of care

Arm type	standard of care

No investigational medicinal product assigned in this arm

Arm title	Non DSA SC (A2)

Arm description:	
Positive non- Donor specific antibodies Standard of care	
Arm type	standard of care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	DSA BLC (B1)	DSA SC (A1)	Non-DSA BLC (B2)
Started	106	92	427
Completed	97	83	374
Not completed	9	9	53
randomised in error	-	-	-
Lost to follow-up	9	9	53

Number of subjects in period 1	Neg Unblinded (D)	Neg Blinded (C)	Non DSA SC (A2)
Started	495	526	391
Completed	421	450	344
Not completed	74	76	47
randomised in error	-	2	-
Lost to follow-up	74	74	47

Baseline characteristics

Reporting groups	
Reporting group title	DSA BLC (B1)
Reporting group description:	
Positive for Donor Specific Antibodies Biomarker Led Care	
Reporting group title	DSA SC (A1)
Reporting group description:	
Positive Donor specific antibodies blinded standard care	
Reporting group title	Non-DSA BLC (B2)
Reporting group description:	
Positive non- Donor specific antibodies Biomarker Led Care	
Reporting group title	Neg Unblinded (D)
Reporting group description:	
HLA Ab negative unblinded standard of care	
Reporting group title	Neg Blinded (C)
Reporting group description:	
HLA ab negative blinded standard of care	
Reporting group title	Non DSA SC (A2)
Reporting group description:	
Positive non- Donor specific antibodies Standard of care	

Reporting group values	DSA BLC (B1)	DSA SC (A1)	Non-DSA BLC (B2)
Number of subjects	106	92	427
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	46.8	48.1	50.3
standard deviation	± 14.0	± 13.7	± 12.6
Gender categorical Units: Subjects			
Female	20	26	176
Male	86	66	251

Reporting group values	Neg Unblinded (D)	Neg Blinded (C)	Non DSA SC (A2)
Number of subjects	495	526	391

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	51.0	51.1	49.4
standard deviation	± 13.3	± 12.7	± 12.7
Gender categorical Units: Subjects			
Female	123	145	152
Male	372	381	239

Reporting group values	Total		
Number of subjects	2037		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	642		
Male	1395		

End points

End points reporting groups

Reporting group title	DSA BLC (B1)
Reporting group description:	
Positive for Donor Specific Antibodies Biomarker Led Care	
Reporting group title	DSA SC (A1)
Reporting group description:	
Positive Donor specific antibodies blinded standard care	
Reporting group title	Non-DSA BLC (B2)
Reporting group description:	
Positive non- Donor specific antibodies Biomarker Led Care	
Reporting group title	Neg Unblinded (D)
Reporting group description:	
HLA Ab negative unblinded standard of care	
Reporting group title	Neg Blinded (C)
Reporting group description:	
HLA ab negative blinded standard of care	
Reporting group title	Non DSA SC (A2)
Reporting group description:	
Positive non- Donor specific antibodies Standard of care	

Primary: Time to Graft Failure

End point title	Time to Graft Failure[1]
End point description:	
Time to graft failure in HLA Ab positive patients randomized to biomarker-led treatment groups vs. time to graft failure in HLA Ab positive patients randomized to the control (standard care) group. Graft failure was defined as re-starting dialysis or requiring a new transplant.	
End point type	Primary
End point timeframe:	
Date of recruitment to month 92.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see separate attachment

End point values	DSA BLC (B1)	DSA SC (A1)	Non-DSA BLC (B2)	Neg Unblinded (D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	106	91	427	495
Units: Number of Graft Failures				
0-1 years	5	1	2	2
1-2 years	6	3	6	6
2-3 years	3	4	6	3
3-4 years	0	2	5	10
4-5 years	3	1	4	0
5-6 years	2	0	0	1
6-7 years	0	0	0	0

End point values	Neg Blinded (C)	Non DSA SC (A2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	391		
Units: Number of Graft Failures				
0-1 years	1	1		
1-2 years	6	8		
2-3 years	9	4		
3-4 years	5	5		
4-5 years	7	2		
5-6 years	0	2		
6-7 years	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: AEs were collected from start of treatment to month 32	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	Body System Code
Dictionary version	1

Reporting groups	
Reporting group title	DSA BLC (B1)
Reporting group description: Positive for Donor Specific Antibodies Biomarker Led Care	
Reporting group title	DSA SC (A1)
Reporting group description: Positive Donor specific antibodies blinded standard care	
Reporting group title	Non-DSA BLC (B2)
Reporting group description: Positive non- Donor specific antibodies Biomarker Led Care	
Reporting group title	Neg Unblinded (D)
Reporting group description: HLA Ab negative unblinded standard of care	
Reporting group title	Neg Blinded (C)
Reporting group description: HLA ab negative blinded standard of care	
Reporting group title	Non DSA SC (A2)
Reporting group description: Positive non- Donor specific antibodies Standard of care	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see attachment that includes a summary of adverse events

Serious adverse events	DSA BLC (B1)	DSA SC (A1)	Non-DSA BLC (B2)
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 106 (24.53%)	18 / 92 (19.57%)	93 / 427 (21.78%)
number of deaths (all causes)	6	3	37
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 92 (0.00%)	3 / 427 (0.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
other			

subjects affected / exposed	5 / 106 (4.72%)	3 / 92 (3.26%)	25 / 427 (5.85%)
occurrences causally related to treatment / all	2 / 6	0 / 3	5 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Immunological			
subjects affected / exposed	0 / 106 (0.00%)	0 / 92 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	5 / 106 (4.72%)	2 / 92 (2.17%)	13 / 427 (3.04%)
occurrences causally related to treatment / all	1 / 6	0 / 2	5 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychological			
subjects affected / exposed	0 / 106 (0.00%)	0 / 92 (0.00%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	4 / 106 (3.77%)	0 / 92 (0.00%)	13 / 427 (3.04%)
occurrences causally related to treatment / all	3 / 8	0 / 0	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neurological			
subjects affected / exposed	1 / 106 (0.94%)	0 / 92 (0.00%)	3 / 427 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haematological			
subjects affected / exposed	2 / 106 (1.89%)	3 / 92 (3.26%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	1 / 2	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Eyes, ear, nose, throat			

subjects affected / exposed	0 / 106 (0.00%)	1 / 92 (1.09%)	2 / 427 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	6 / 106 (5.66%)	5 / 92 (5.43%)	14 / 427 (3.28%)
occurrences causally related to treatment / all	1 / 9	0 / 5	2 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic			
subjects affected / exposed	0 / 106 (0.00%)	0 / 92 (0.00%)	3 / 427 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatological			
subjects affected / exposed	1 / 106 (0.94%)	0 / 92 (0.00%)	3 / 427 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Genito-urinary/renal			
subjects affected / exposed	14 / 106 (13.21%)	11 / 92 (11.96%)	38 / 427 (8.90%)
occurrences causally related to treatment / all	3 / 29	0 / 17	14 / 53
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Endocrine			
subjects affected / exposed	1 / 106 (0.94%)	0 / 92 (0.00%)	3 / 427 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	1 / 106 (0.94%)	2 / 92 (2.17%)	6 / 427 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Neg Unblinded (D)	Neg Blinded (C)	Non DSA SC (A2)

Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 492 (17.28%)	88 / 526 (16.73%)	65 / 391 (16.62%)
number of deaths (all causes)	52	50	28
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia			
subjects affected / exposed	1 / 492 (0.20%)	1 / 526 (0.19%)	0 / 391 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
other			
subjects affected / exposed	15 / 492 (3.05%)	23 / 526 (4.37%)	17 / 391 (4.35%)
occurrences causally related to treatment / all	0 / 18	0 / 26	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Immunological			
subjects affected / exposed	0 / 492 (0.00%)	0 / 526 (0.00%)	0 / 391 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	11 / 492 (2.24%)	17 / 526 (3.23%)	12 / 391 (3.07%)
occurrences causally related to treatment / all	0 / 12	0 / 24	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychological			
subjects affected / exposed	0 / 492 (0.00%)	0 / 526 (0.00%)	2 / 391 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	14 / 492 (2.85%)	6 / 526 (1.14%)	6 / 391 (1.53%)
occurrences causally related to treatment / all	0 / 17	0 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Neurological			
subjects affected / exposed	3 / 492 (0.61%)	4 / 526 (0.76%)	2 / 391 (0.51%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haematological			
subjects affected / exposed	4 / 492 (0.81%)	5 / 526 (0.95%)	2 / 391 (0.51%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Eyes, ear, nose, throat			
subjects affected / exposed	0 / 492 (0.00%)	0 / 526 (0.00%)	2 / 391 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	16 / 492 (3.25%)	26 / 526 (4.94%)	10 / 391 (2.56%)
occurrences causally related to treatment / all	0 / 20	0 / 35	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic			
subjects affected / exposed	1 / 492 (0.20%)	1 / 526 (0.19%)	0 / 391 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatological			
subjects affected / exposed	3 / 492 (0.61%)	5 / 526 (0.95%)	3 / 391 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Genito-urinary/renal			
subjects affected / exposed	29 / 492 (5.89%)	31 / 526 (5.89%)	23 / 391 (5.88%)
occurrences causally related to treatment / all	0 / 44	0 / 51	0 / 37
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Endocrine			
subjects affected / exposed	4 / 492 (0.81%)	0 / 526 (0.00%)	4 / 391 (1.02%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	6 / 492 (1.22%)	5 / 526 (0.95%)	2 / 391 (0.51%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DSA BLC (B1)	DSA SC (A1)	Non-DSA BLC (B2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 106 (0.00%)	0 / 92 (0.00%)	0 / 427 (0.00%)

Non-serious adverse events	Neg Unblinded (D)	Neg Blinded (C)	Non DSA SC (A2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 492 (0.00%)	0 / 526 (0.00%)	0 / 391 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	The trial was temporarily suspended during the first COVID-19 pandemic (20/03/2020 – 01/09/2020), and date for completion of primary endpoint data collection extended from June 2020 to November 2020.	01 September 2020

Notes:

Limitations and caveats

None reported