



Clinical trial results:

Multi-centre, randomised, open-label, blinded endpoint assessed, trial of corticosteroids plus intravenous immunoglobulin (IVIG) and aspirin, versus IVIG and aspirin for prevention of coronary artery aneurysms in Kawasaki disease

(KD-CAAP: Kawasaki Disease Coronary Artery Aneurysm Prevention trial)

Summary

EudraCT number	2019-004433-17
Trial protocol	GB BE EE SE FI ES DE NL IT AT CZ
Global end of trial date	21 October 2024

Results information

Result version number	v1 (current)
This version publication date	01 August 2025
First version publication date	01 August 2025

Trial information

Trial identification

Sponsor protocol code	124210
-----------------------	--------

Additional study identifiers

ISRCTN number	ISRCTN71987471
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	90 High Holborn , London, United Kingdom,
Public contact	Clinical Trial Manager, MRC CTU at UCL, mrcctu.kdcaap@ucl.ac.uk
Scientific contact	Clinical Trial Manager, MRC CTU at UCL, mrcctu.kdcaap@ucl.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2024
Global end of trial reached?	Yes
Global end of trial date	21 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the combination of corticosteroid and IVIG/aspirin reduce the rate of heart complications in children/adolescents with Kawasaki disease across Europe compared with IVIG/aspirin alone?

Protection of trial subjects:

Inclusion/exclusion criteria and follow-up visits were carefully chosen to minimise the risk to trial subjects. Participants were closely monitored including daily assessments from days 1-5. The clinical examination explicitly prompted for symptoms related to possible drug toxicities. Rescue treatment was permitted at any time at the clinician's discretion and investigators were prompted to consider rescue at day 5 if temperature and CRP were still high.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2021
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	France: 8
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	103
EEA total number of subjects	56

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	35
Children (2-11 years)	67
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

106 screened.

Period 1

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

Blinding implementation details:

Echocardiograms were reviewed centrally by a paediatric echocardiographer blinded to treatment group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Standard of care IVIG and aspirin.

Arm type	Active comparator
Investigational medicinal product name	IVIG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2mg/kg given as per local standard of care. A second dose may be given on day 2.

Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/kg/day administered orally until child is afebrile for at least 48 hours, reducing to 3-5mg/kg/day until at least 21 days after the resolution of fever.

Arm title	Experimental
------------------	--------------

Arm description:

Standard of care IVIG and aspirin as in the control arm, plus corticosteroids (prednisolone or methylprednisolone).

Arm type	Experimental
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Soluble tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Initial dose of 2mg/kg/day. Tapering allowed from day 5 onwards providing there is resolution of fever, and should be completed over 15 days in 5 day steps from 2 to 1 to 0.5mg/kg/day, and then to 0.

Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Solvent for...
Routes of administration	Intravenous use

Dosage and administration details:

If oral prednisolone is not tolerated, IV methylprednisolone may be given at equivalent doses (initial dose of 1.6mg/kg/day).

Investigational medicinal product name	IVIG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2mg/kg given as per local standard of care. A second dose may be given on day 2.

Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/kg/day administered orally until child is afebrile for at least 48 hours, reducing to 3-5mg/kg/day until at least 21 days after the resolution of fever.

Number of subjects in period 1	Control	Experimental
Started	53	50
Completed	50	48
Not completed	3	2
Withdrawn	2	-
Missed final visit	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Control
Reporting group description:	
Standard of care IVIG and aspirin.	
Reporting group title	Experimental
Reporting group description:	
Standard of care IVIG and aspirin as in the control arm, plus corticosteroids (prednisolone or methylprednisolone).	

Reporting group values	Control	Experimental	Total
Number of subjects	53	50	103
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	20	15	35
Children (2-11 years)	33	34	67
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at last birthday			
Units: years			
median	2	2	
inter-quartile range (Q1-Q3)	1 to 3	1 to 4	-
Gender categorical			
Units: Subjects			
Female	22	21	43
Male	31	29	60
Type of Kawasaki disease			
Complete or incomplete Kawasaki disease			
Units: Subjects			
Complete	49	47	96
Incomplete	4	3	7
Bilateral non purulent conjunctivitis			
Bilateral non purulent conjunctivitis present at randomisation			
Units: Subjects			
Yes	50	49	99
No	3	1	4
Cervical lymphadenopathy			
Cervical lymphadenopathy present at baseline			
Units: Subjects			
Yes	40	39	79
No	13	11	24

Polymorphous skin rash			
Polymorphous skin rash present at baseline			
Units: Subjects			
Yes	53	47	100
No	0	3	3
Changes in lips or mucosa			
Changes in lips or mucosa (strawberry tongue, red cracked lips, diffuse erythematous oropharynx) present at baseline			
Units: Subjects			
Yes	52	47	99
No	1	3	4
Extremity changes			
Extremity changes (erythema, oedema of palms and soles in initial phase, and at convalescent stage skin peeling) present at baseline			
Units: Subjects			
Yes	39	41	80
No	14	9	23
Duration of fever at randomisation			
Units: day			
median	7	7	
inter-quartile range (Q1-Q3)	6 to 9	6 to 8	-
Weight			
Units: kilogram(s)			
median	14	15	
inter-quartile range (Q1-Q3)	11 to 17	13 to 18	-
Heart rate			
Data available for 102 participants.			
Units: beats per minute			
median	124	133	
inter-quartile range (Q1-Q3)	107 to 142	115 to 146	-
Temperature			
Units: celsius temperature			
median	38.4	38.3	
inter-quartile range (Q1-Q3)	36.9 to 39.1	37.4 to 38.8	-
CRP			
C-reactive protein at baseline. Data available for 102 participants.			
Units: mg/L			
median	112	148	
inter-quartile range (Q1-Q3)	70 to 194	86 to 220	-
Sodium			
Data available for 97 participants.			
Units: mmol/L			
median	135	136	
inter-quartile range (Q1-Q3)	133 to 137	133 to 138	-
Potassium			
Data available for 90 participants.			
Units: mmol/L			
median	4.1	4.2	
inter-quartile range (Q1-Q3)	3.9 to 4.6	3.8 to 4.5	-
Height/length			
Units: centimetre			
median	92	98	

inter-quartile range (Q1-Q3)	82 to 104	87 to 110	-
Albumin			
Data available for 90 participants.			
Units: gram(s)/litre			
median	30	29	
inter-quartile range (Q1-Q3)	25 to 34	24 to 31	-
Haemoglobin			
Data available for 96 participants.			
Units: gram(s)/litre			
median	104	101	
inter-quartile range (Q1-Q3)	96 to 112	96 to 113	-
White cell count			
Data available for 96 participants.			
Units: thousand cells/microlitre			
median	14	13	
inter-quartile range (Q1-Q3)	10 to 17	9 to 15	-
Platelet count			
Data available for 95 participants.			
Units: thousand cells/microlitre			
median	388	322	
inter-quartile range (Q1-Q3)	296 to 421	270 to 463	-
Erythrocyte sedimentation rate			
Data available for 57 participants.			
Units: millimetres/hour			
median	88	81	
inter-quartile range (Q1-Q3)	56 to 110	51 to 106	-
Maximum measurement of luminal diameter			
Maximum measurement of LAD, LMCA, or RCA artery. Baseline echocardiograms were optional but data collected where performed. Data available for 58 participants.			
Units: millimetre(s)			
median	2.3	2.4	
inter-quartile range (Q1-Q3)	2.0 to 2.6	2.0 to 2.5	-
Maximum z-score of luminal diameter			
Maximum z-score of RCA, LAD or LMCA artery based on Lopez formula. Baseline echocardiograms were optional but data collected where performed. Data available for 58 participants.			
Units: z-score			
median	1.5	0.7	
inter-quartile range (Q1-Q3)	0.9 to 2.2	0.2 to 1.5	-
Systolic blood pressure			
Data available for 99 participants.			
Units: mmHg			
median	100	98	
inter-quartile range (Q1-Q3)	91 to 108	93 to 104	-
Diastolic blood pressure			
Data available for 99 participants.			
Units: mmHg			
median	60	60	
inter-quartile range (Q1-Q3)	52 to 68	54 to 67	-

End points

End points reporting groups

Reporting group title	Control
Reporting group description: Standard of care IVIG and aspirin.	
Reporting group title	Experimental
Reporting group description: Standard of care IVIG and aspirin as in the control arm, plus corticosteroids (prednisolone or methylprednisolone).	

Primary: Number of children developing coronary artery aneurysm by week 12

End point title	Number of children developing coronary artery aneurysm by week 12
End point description: CAA is defined as any of - luminal diameter >3.0 mm in a child <5 years - luminal diameter >4.0 mm in a child/adolescent ≥5 years - internal diameter of a segment at least 1.5 times that of an adjacent segment or when a luminal contour is clearly irregular - luminal internal diameter Z-score of ≥2.5 Z-scores are calculated based on the Lopez method.	
End point type	Primary
End point timeframe: Any CAA identified up to 12 weeks from randomisation, on scheduled echocardiograms (weeks 1, 2, 6 and 12) or additional unscheduled scans.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: Number of children				
CAA	12	12		
No CAA	41	38		

Statistical analyses

Statistical analysis title	Bayesian model with uninformative prior
Statistical analysis description: Difference in risk of developing a CAA estimated from Bayesian logistic regression with uninformative prior for treatment effect. Adjusted for randomisation stratification factors (age in categories <1, ≥1 year; sex; country).	
Comparison groups	Experimental v Control

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	16.1

Notes:

[1] - Note: there is no confidence interval, the interval reported is a 95% equal-tailed credible interval.

Statistical analysis title	Bayesian model with enthusiastic prior
-----------------------------------	--

Statistical analysis description:

Difference in risk of developing a CAA estimated from Bayesian logistic regression with enthusiastic prior for treatment effect (based on expected reduction of 12% in experimental arm). Adjusted for randomisation stratification factors (age in categories <1, >=1 year; sex; country).

Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
Parameter estimate	Risk difference (RD)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.4
upper limit	3.8

Notes:

[2] - Note: there is no confidence interval, the interval reported is a 95% equal-tailed credible interval.

Statistical analysis title	Bayesian model with skeptical prior
-----------------------------------	-------------------------------------

Statistical analysis description:

Difference in risk of developing a CAA estimated from Bayesian logistic regression with a skeptical prior for treatment effect (centred around no difference). Adjusted for randomisation stratification factors (age in categories <1, >=1 year; sex; country).

Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	11.3

Notes:

[3] - Note: there is no confidence interval, the interval reported is a 95% equal-tailed credible interval.

Statistical analysis title	Unadjusted Bayesian model with uninformative prior
Statistical analysis description:	
Difference in risk of developing a CAA estimated from unadjusted Bayesian logistic regression with uninformative prior for treatment effect.	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	17.8

Notes:

[4] - Note: there is no confidence interval, the interval reported is a 95% equal-tailed credible interval.

Statistical analysis title	Frequentist model
Statistical analysis description:	
Difference in risk of developing a CAA estimated from logistic regression. Adjusted for age in categories <1, >=1 year, and sex.	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	16.8

Primary: Average maximum z-score of RCA or LAD across weeks 1, 2 and 6

End point title	Average maximum z-score of RCA or LAD across weeks 1, 2 and 6
End point description:	
An average estimate across weeks 1, 2, and 6 of the maximum of the Z-score of the internal diameters of the proximal right coronary artery or left anterior descending coronary artery, adjusted for rescue treatment.	
End point type	Primary
End point timeframe:	
Averaged across week 1, 2, and 6.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: z-score				
arithmetic mean (confidence interval 95%)	0.6 (0.4 to 0.9)	0.7 (0.4 to 0.9)		

Statistical analyses

Statistical analysis title	GEE with time-updated IPTW
Statistical analysis description:	
Mean difference calculated from generalised estimating equation with independent correlation structure, adjusting for rescue treatment using weights based on baseline (age, CRP, temperature) and time-updated factors (CRP, temperature). Model also adjusts for randomisation stratification factors (age in categories <1, >=1; sex; country), and maximum z-score as baseline (grouped as below median, above median, or missing). Z-scores transformed $\ln(x+1.40)$ for normality prior to analysis.	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Generalised estimating equation
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Statistical analysis title	GEE with baseline IPTW
Statistical analysis description:	
Mean difference calculated from generalised estimating equation with independent correlation structure, adjusting for rescue treatment using weights based on baseline factors only (age, CRP, temperature). Model also adjusts for randomisation stratification factors (age in categories <1, >=1; sex; country), and maximum z-score as baseline (grouped as below median, above median, or missing). Z-scores transformed $\ln(x+1.40)$ for normality prior to analysis.	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Generalised estimating equation
Parameter estimate	Mean difference (final values)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Statistical analysis title	Intention to treat estimate
-----------------------------------	-----------------------------

Statistical analysis description:

Mean difference calculated from generalised estimating equation with independent correlation structure, with no adjustment for rescue treatment. Model adjusts for randomisation stratification factors (age in categories <1, >=1; sex; country), and maximum z-score as baseline (grouped as below median, above median, or missing). Z-scores transformed $\ln(x+1.40)$ for normality prior to analysis.

Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Generalised estimating equation
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Secondary: Number of children developing CAA with stricter definition of luminal internal diameter z-score >=2.5

End point title	Number of children developing CAA with stricter definition of luminal internal diameter z-score >=2.5
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Up to week 12.

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: number	10	8		

Statistical analyses

Statistical analysis title	Logistic regression
Statistical analysis description: Percentage and difference between arms estimated from margins following logistic regression, adjusted for randomisation stratification factors (except country due to small numbers).	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	11

Secondary: Number of children receiving rescue treatment

End point title	Number of children receiving rescue treatment
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to week 12.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: participants				
Received rescue treatment	17	8		
No rescue treatment	36	42		

Statistical analyses

Statistical analysis title	Logistic regression
Statistical analysis description: Percentage and difference between arms estimated from margins following logistic regression, adjusted for randomisation stratification factors (except country due to small numbers).	
Comparison groups	Control v Experimental

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32
upper limit	0

Secondary: Number of children receiving second dose of IVIG

End point title	Number of children receiving second dose of IVIG
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to week 12.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: participants				
Received second IVIG dose	20	9		
No second IVIG dose	33	41		

Statistical analyses

Statistical analysis title	Logistic regression
Statistical analysis description:	
	Percentage and difference between arms estimated from margins following logistic regression, adjusted for randomisation stratification factors (except country due to small numbers).
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-20

Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	-3

Secondary: Duration of fever after enrolment

End point title	Duration of fever after enrolment
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation until week 12.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: day				
median (inter-quartile range (Q1-Q3))	1 (1 to 2)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	Duration of fever after enrolment
Statistical analysis description:	
Subhazard ratio and p-value from competing risks model with death as competing risk (prespecified in SAP; although there were no deaths)	
Comparison groups	Control v Experimental
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Competing risks model
Parameter estimate	Subhazard ratio
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.7

Secondary: Mean CRP across day 1 - week 2

End point title	Mean CRP across day 1 - week 2
End point description:	
End point type	Secondary
End point timeframe:	
Averaged across day 1, 2, 3, 4, 5, and week 1 and week 2 visits.	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	50		
Units: milligram(s)/litre				
arithmetic mean (confidence interval 95%)	15 (14 to 16)	13 (12 to 14)		

Statistical analyses

Statistical analysis title	Mean CRP across day 1-week 2
Statistical analysis description:	
Mean CRP across day 1-week 2 estimated using GEE with independent correlation structure, adjusted for stratification factors (age in categories <1, >=1; sex; country). CRP values transformed log 2 before analysis.	
Comparison groups	Control v Experimental
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Generalised estimating equation
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 12 weeks

Adverse event reporting additional description:

Details of adverse events were recorded at each follow up visit. SAEs, grade 3/4 AEs, AEs of any grade that lead to change in IVIG, aspirin or prednisolone/methylprednisolone, and clinical AEs of any grade judged definitely/probably/possibly related to IVIG, aspirin or prednisolone/methylprednisolone were recorded.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.1
--------------------	------

Reporting groups

Reporting group title	Control
-----------------------	---------

Reporting group description:

Standard of care IVIG and aspirin.

Reporting group title	Experimental
-----------------------	--------------

Reporting group description:

Standard of care IVIG and aspirin as in the control arm, plus corticosteroids (prednisolone or methylprednisolone).

Serious adverse events	Control	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 53 (5.66%)	7 / 50 (14.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Staphylococcus aureus test positive			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	0 / 53 (0.00%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm of coronary vessels			

subjects affected / exposed	1 / 53 (1.89%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery aneurysm			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial depression			
subjects affected / exposed	1 / 53 (1.89%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 53 (1.89%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tachypnoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Kawasaki's disease			

subjects affected / exposed	1 / 53 (1.89%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection susceptibility increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Control	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 53 (50.94%)	18 / 50 (36.00%)	
Investigations			
Alanine aminotransferase high			
subjects affected / exposed	3 / 53 (5.66%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Albumin low			
subjects affected / exposed	3 / 53 (5.66%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Aspartate aminotransferase high			
subjects affected / exposed	2 / 53 (3.77%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 50 (0.00%)	
occurrences (all)	2	0	

CRP increased subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 50 (2.00%) 2	
Creatinine high subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 6	2 / 50 (4.00%) 2	
Haemoglobin low subjects affected / exposed occurrences (all)	14 / 53 (26.42%) 15	5 / 50 (10.00%) 6	
Phosphate low subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	4 / 50 (8.00%) 4	
Vascular disorders Nose bleed subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	1 / 50 (2.00%) 2	
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	0 / 50 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2020	Addition of the word 'additional' oral steroids to the experimental group, Clarification that 'clinical' adverse events of any grade related to IVIG, aspirin or corticosteroids should be collected, Removal the following sentence related to IVIG and aspirin 'They are supplied to the trial participants according the protocol but are NOT under investigation.', Update to the Funders grant agreement number, Clarification that Echocardiograms and ECGs completed on a scheduled visit should be collected although they are not mandatory for the trial, Clarification that IVIG can be infused dependent as per standard of care within the member state, Typographical error for reason that randomisation will be stratified, should be country rather than site.
15 May 2020	Addition of the ISRCTN number, Amendment to the trial compliance statement to allow local national law requirements to be met in EU countries and clarification that in terms of confidentiality GDPR will be followed, Updates to Trial Administration – addition of CTU Data Manager and amendment to the address for the Nursing co-investigator, Amendment of the duration of aspirin given to participants to at least 21 days, Clarification of the 48 hour assessment should be performed within the day 2 assessment, Clarification that the maximum daily temperature will be collected from Day 5 until discharge or until the child/adolescent is afebrile for 2 calendar days, Clarification on the documents required at site assessment, Clarification of the inclusion criteria that the child/adolescent must be below the age of country specific consent for the duration of the trial, Minor typographical amendments to make the wording consistent within the inclusion criteria, Removal of randomisations being completed by the CTU over the phone, Information on the timing of the first dose of corticosteroids, Amendment to the trial IMP dispensing and accountability requirements, Clarification of the data collected for treatment of KD, Addition that adherence to aspirin will be collected using standardised diaries in the control and experimental group, Clarification that echocardiograms collected from any unscheduled timepoints will be centrally assessed, Clarification that only overdose of IMP which results in clinical symptoms of any grade is a notifiable event, Addition of detail regarding the use of IVIG and aspirin during pregnancy, Amendment to the TMG membership.

07 April 2021	Addition of details where queries should be sent relating to the sponsorship of the trial, Update to the details within Trial Administration include the addition of the emergency contact details for Paul Brogan and Despina Eleftheriou, addition of a trial manager to the CTU Staff and Affiliates, update to the address and contact details for Cardiology co-investigator Professor Robert Tulloh, Addition that visits maybe conducted via telephone, Clarification that the dose of aspirin should not be reduced until the participant has been afebrile for at least 48 hours, EudraCT# added, Update to the wording ancillary studies to substudies, Addition of urine or blood pregnancy test for adolescents who are menstruating, and exclusion criteria as pregnant or breastfeeding, Removal of LDL and HbA1c collection, Update to the volume of research blood samples collected, Update to the time points weight is collected at, Update to remove collection of temperature from the axilla throughout the protocol, Clarification that if the CHU9D is not available in the local language it does not have to be completed, Clarification that the recommendations for the volume of blood collected relate to the research specific bloods, Addition of Section 1.6 related to the benefit-risk assessment for the trial, Addition of 'or known phenylketonuria to aspartame used in a formulation in an infant less than 12 weeks.' to exclusion 7. criteria, Rationale for collecting date of birth added, The details regarding collection of weight for dosing has been moved from 5.3.1 to 5, Clarification that there are no trial specific temperature monitoring requirements for the IMP, Inclusion of a +/- 20% flexibility in the dosing of IVIG and aspirin, Removal of wording surrounding the regular weight collection included in error, Clarification that enough IMP should be dispensed to reach the participants next visit or to allow the completion their duration of corticosteroids, Addition of mitigation for provision o
22 October 2021	EudraCT number added to cover and general information, Addition of (Fortaleza, Brazil, October 2013) to the Declaration of Helsinki meeting which the trial is run in accordance with, Update to MRC CTU staff, Update to exclusion criteria 10 to include active influenza infection, Removal or wording 'In particular, the investigator must ensure that the children's anonymity will be maintained and that their identities are protected from unauthorised parties.', Update from a Standard Operating Procedure to Guidance, Update wording in section 9.4 to make it consistent with the wording changed in Protocol v4.0, Oversight and Trial Committees Section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported