Clinical trial results:
Low-dose colchicine for secondary prevention of cardiovascular disease

Summary

EudraCT number	2015-005568-40
Trial protocol	NL
Global end of trial date	28 April 2020

Results information

Result version number	v1 (current)
This version publication date	30 June 2021
First version publication date	30 June 2021

Trial information

Trial identification

Sponsor protocol code	LoDoCo2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	WCN
Sponsor organisation address	Moreelsepark 1, Utrecht, Netherlands,
Public contact	Chair WCN, Werkgroep Cardiologische centra Nederland, secretariaat@wcnnet.nl
Scientific contact	Chair WCN, Werkgroep Cardiologische centra Nederland, secretariaat@wcnnet.nl

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	01 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2020
Global end of trial reached?	Yes
Global end of trial date	28 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate clinical efficacy of treatment with colchicine 0.5mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of the composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven revascularization.

Protection of trial subjects:

Colchicine 0.5mg once daily is the reduced dosage recommended by the 2012 American College of Rheumatology Guidelines for Management of Gout and the FDA prescription information for Colcrys in patients with impaired renal function and for patients with concomitant use of CYP3A4 or P-glycoprotein inhibitors. (70, 71)
A 30-day open label colchicine run-in period will largely filter out those with side effects occurring after initiating colchicine. By only including patients with normal renal function (eGFR ≥ 50 ml/min/1.73m2 or a serum creatinine > 150 µmol/L) and by using low-dose colchicine, adverse effects are likely to be reduced to a minimum as in the pilot LoDoCo trial.
General practitioners and pharmacies will be informed on the study participation of their patients. They will be asked to report events or adverse reactions to the trial medication. Second, they will be asked to interrupt the trial medication during administration of known CYP3A4 inhibitors and monitor renal function closely in situations where it is expected that this might be impaired (e.g. diarrhoea or the start of nephrotoxic medicine).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
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	Netherlands: 4084
Country: Number of subjects enrolled	Australia: 2444
Worldwide total number of subjects	6528
EEA total number of subjects	4084

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3678
From 65 to 84 years	2850
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started in August 2014 in Australia and October 2016 in The Netherlands. Recruitment ended December 3rd 2018 when the 5522th participant was randomized in The Netherlands.

Pre-assignment

Screening details:

On the assumption that 10% of participants would report early intolerance to therapy, the trial aimed to enrol 6053 screened patients, expecting 5447 to be randomized (divided over both continents) and then followed for a median of 3 years.

Period 1

Period 1 title	Run in
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

30 day open label run-in.

Arms

Arm title	colchicine 0.5mg

Arm description:

Open label run-in

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

Dosage and administration details:

0.5 mg once daily

Number of subjects in period 1	colchicine 0.5mg
Started	6528
Completed	5522
Not completed	1006
intolerance or compliance issues	1006

Period 2

Period 2 title	Randomised
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:
double blind placebo controlled

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:
once daily

Arm title	colchicine

Arm description: -

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

Dosage and administration details:
0.5 mg once daily

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

Dosage and administration details:
once daily

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics and study details are reported on the randomized population (intention to treat). Randomisation was proceded by an open-label run-in.

Number of subjects in period 2[2]	Placebo	colchicine
Started	2760	2762
Completed	2760	2762

Notes:

[2] - 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: Baseline characteristics and study details are reported on the randomized population (intention to treat). Randomisation was proceded by an open-label run-in

Baseline characteristics

Reporting groups	
Reporting group title	Randomised

Reporting group description: -

Reporting group values	Randomised	Total	
Number of subjects	5522	5522	
Age categorical Units: Subjects			
Adults (18-64 years)	3098	3098	
Adults (65-82 years)	2424	2424	
Age continuous Units: years			
arithmetic mean	65.8		
standard deviation	± 8.4	-	
Gender categorical Units: Subjects			
Female	846	846	
Male	4676	4676	

End points

End points reporting groups

Reporting group title	colchicine 0.5mg
Reporting group description: Open label run-in	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	colchicine
Reporting group description: -	

Primary: death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization

End point title	death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization[1]
End point description:	
End point type	Primary
End point timeframe: time from randomisation to first primary event.	

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: The statistical analysis can be found in the appendix of the main paper

End point values	Placebo	colchicine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	164		
Units: first events	187	164		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: per protocol targeted AE collection from signing of ICF until final visit	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	2020

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

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: reporting and description can be found in the mainpaper

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2020	all amendments have been specified in the protocol. Version 2.7 is the final version of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31706144

http://www.ncbi.nlm.nih.gov/pubmed/32865380