Clinical trial results:
Xanthine oxidase inhibition for improvement of long-term outcomes following ischaemic stroke and transient ischaemic attack (XILO-FIST).

Summary

EudraCT number	2013-004235-77
Trial protocol	GB
Global end of trial date	02 March 2021

Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022

Trial information

Trial identification

Sponsor protocol code	XILO-FIST

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02122718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Grahamston Road, Paisley, United Kingdom, PA2 7DE
Public contact	Dr Maureen Travers, NHS Greater Glasgow and Clyde, 0044 141 314 4012, maureen.travers@ggc.scot.nhs.uk
Scientific contact	Dr Maureen Travers, NHS Greater Glasgow and Clyde, 0044 141 314 4012, maureen.travers@ggc.scot.nhs.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
Public contact	Dr Debra Stuart, University of Glasgow, 0044 141 330 4539, Debra.Stuart@glasgow.ac.uk
Scientific contact	Dr Debra Stuart, University of Glasgow, 0044 141 330 4539, Debra.Stuart@glasgow.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	23 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2021
Global end of trial reached?	Yes
Global end of trial date	02 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To establish whether a two year course of allopurinol 300 mg twice daily reduces WMH progression after ischaemic stroke.

Protection of trial subjects:

IMP Dose selection - A dose of 600 mg daily had been studied in numerous recent trials in patients with ischaemic heart disease and patients at high cardiovascular risk. This dose appears to have greater cardiovascular benefits than lower doses. In these trials there were no safety concerns, even though some had renal dysfunction. The risk of severe hypersensitivity reactions seems to be confined to the first weeks of treatment. We therefore chose to study a lower dose initially, and to instruct participants to stop medication immediately if they develop a rash and will not up-titrate participants whose renal function is poor (defined as estimated glomerular filtration rate (eGFR)<60 mL/min) or when there are concerns regarding hepatic function.

COVID and IMP exposure: We extended the maximum duration of IMP that a participant can take from 2 years (104 weeks) by an additional 6 months (26 weeks) in response to the temporary shut-down of face to face visits at many sites in response to the COVID-19 pandemic. Given by this point participants remaining on study drug will have been taking it for 2-years without significant side-effects requiring them to stop then the additional risk of 6-months exposure is limited. Dispensing was carried out without further blood tests but clinically available blood tests were reviewed and all participants contacted ahead of additional dispensing timepoint to ensure it was safe to continue.

Background therapy:

Participant treated with standard 2ndry prevention method (98% on antiplatement)

Evidence for comparator:

N/A

Actual start date of recruitment	02 February 2015
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: 464
Worldwide total number of subjects	464
EEA total number of subjects	0

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)	224
From 65 to 84 years	237
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants recruited from 25th May 2015. Participants recruited from acute stroke services.

Pre-assignment

Screening details:

Case note review of in-patient / outpatient attendees to the Acute Stroke Service by clinicians.

At baseline screening, dementia will be an exclusion criterion to participation in the study. The assessment of pre-stroke dementia will comprise case-note review for any documented diagnosis of dementia and informant assessment using the 16 item IQC

Period 1

Period 1 title	Full Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Although not possible to obtain an exact active-placebo tablet match, the objective nature of the primary end-points and the use of study specific arrangements maintained blinding address this potential risk.

All participants will be issued with a study card with emergency unblinding information and contact details for the local study team.

Arms

Are arms mutually exclusive?	Yes
Arm title	Allopurinol

Arm description:

Allopurinol 300 mg twice daily for two years

Arm type	Experimental
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	MA04AA01
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first month, a 300 mg daily dose of allopurinol will be taken. All participants will then undergo a dose titration to allopurinol 300 mg twice daily unless creatinine clearance is < 60 ml / minute (based on eGFR and where the dose will be maintained at allopurinol 300 mg daily).

Arm title	Placebo

Arm description:

300 mg placebo twice daily for two years

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:

During the first month, a 300 mg daily dose of placebo will be taken. All participants will then undergo a dose titration to 300 mg twice daily unless creatinine clearance is < 60 ml / minute (based on eGFR and

where the dose will be maintained at 300 mg).

Number of subjects in period 1	Allopurinol	Placebo
Started	232	232
Completed	198	200
Not completed	34	32
Adverse event, serious fatal	5	3
Adverse event, non-fatal	29	29

Baseline characteristics

Reporting groups	
Reporting group title	Full Trial Period

Reporting group description: -

Reporting group values	Full Trial Period	Total	
Number of subjects	464	464	
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	65.7		
standard deviation	± 8.71	-	
Gender categorical Units: Subjects			
Female	145	145	
Male	319	319	

End points

End points reporting groups

Reporting group title	Allopurinol
Reporting group description: Allopurinol 300 mg twice daily for two years	
Reporting group title	Placebo
Reporting group description: 300 mg placebo twice daily for two years	
Subject analysis set title	Primary Endpoint
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants who attended for 2 year MRI.	

Primary: Rotterdam progression Scale

End point title	Rotterdam progression Scale
End point description:	
End point type	Primary
End point timeframe: 24 Months	

End point values	Allopurinol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	189		
Units: 19				
arithmetic mean (standard deviation)	1.3 (± 1.79)	1.5 (± 1.89)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Statistical analysis description: ANCOVA	
Comparison groups	Placebo v Allopurinol
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.173

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.519
upper limit	0.173
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Randomisation to 30 day following end of trial or last IMP dose.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Placebo
Reporting group description: At least 1 serious adverse event	
Reporting group title	Allopurinol
Reporting group description: At least one serious adverse event	

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: The details required to report on the numbers and categories of non-serious adverse events is not available in the data report provided from the data centre as per the Statistical Analysis Plan..
Some non-serious events are referred to in the data report however it's not possible to tease out the details needed to report these here.

Serious adverse events	Placebo	Allopurinol	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 64 (100.00%)	73 / 73 (100.00%)	
number of deaths (all causes)	3	5	
number of deaths resulting from adverse events	3	5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 64 (4.69%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 64 (6.25%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	2 / 64 (3.13%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			

subjects affected / exposed	1 / 64 (1.56%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	10 / 64 (15.63%)	10 / 73 (13.70%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 64 (1.56%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 64 (3.13%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 64 (1.56%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 64 (3.13%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 64 (1.56%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 64 (1.56%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	1 / 64 (1.56%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 64 (0.00%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral hypoperfusion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			

subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post stroke epilepsy			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic function abnormal			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 64 (1.56%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 64 (0.00%)	2 / 73 (2.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Allopurinol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)	0 / 73 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2015	• Inclusion/exclusion - women of child-bearing potential are now excluded, this has been updated due to the new MHRA guidance on contraception. • Safety Reporting text has been updated to be clearer on reporting to the Sponsor. • Correction of minor administrative errors in relation to schedule of events table and study visit text in protocol section 3. • Correction of subsection heading 4.9. • Clarification of sub-study and sub-analysis
21 April 2015	AM03 (Non substantial) Update to the Adverse Event Section reporting in the protocol
24 July 2015	AM05 (Non-Substantial) Protocol, Section 3.4.1: the inclusion criteria for the Cardiac Sub-study has been expanded to include patients with LVH on ECH using one of two scales PIS/ICF: Clarification that an ultrasound OR an ECG may be used to determine LVH (i.e. the change reflects the updated inclusion criteria in the protocol)
17 September 2015	AM08 (Substantial) • Exclusion criteria updated in light of recent publications. Exclusion criteria now include: o 14. eGFR < 60 and of Korean, Han Chinese or Thai descent
07 January 2016	AM09 (Non-Substantial) The Study protocol for this study has been updated from v4.0 to v4.1. The changes were as follows: • Image adjudication committee clarification. • Chief Investigator contact details updated. • Sponsor contact details updated • Pharmacy contact details updated.
15 July 2016	AM12 (Substantial) The addition of food frequency questionnaires. The eligibility criteria has been reformatted to give additional clarification to the data centre –the eligibility criteria has not changed. Updated information for relatives, site specific information is to be placed here.
06 December 2016	AM13 6th Dec 2016 Clarification of sample size required for carotid sub study Change to cardiac sub study eligibility criteria.
30 January 2018	AM20 (Substantial) Addition of the MRI Substudy. Aim is to see whether its possible to detect in blood vessels in people with cerebral small vessel disease and whether other findings such as microinfarcts relate to measures such as cognitive function.

23 April 2018	AM22 (Substantial) This relates to an update to the protocol for the addition of new exclusion criteria. "Korean, Han Chinese or Thai descent unless negative HLA-B*5801 status is known." The update to the exclusion criteria is being made due updated SmPC: The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, 8-15% in the Thai, about 12% in the Korean population. Risk may also be increased due to chronic kidney disease. As it is not logistically possible to screen patients for this allele it was decided that it would be safer to exclude patients from these populations from the study, unless they were already known to be negative for this allele.
03 December 2018	AM26 (Substantial) The eligibility criteria of the 7T MRI sub study has been clarified. For the main study protocol there have been multiple administrative changes and clarification of image reviewers.
31 July 2019	AM27 (Substantial) 1. To remove the secondary endpoint 'to establish whether allopurinol reduces LVH after ischaemic stroke' , and terminate the cardiac sub-study. The assessment of Left Ventricular Hypertrophy (LVH) was to be obtained from cardiac MRIs done on a subgroup of participants at week 4 and week 104. The sub-study had a target of 100 participants, however only recruited 26 participants, and recruitment to the main study is now completed. There is therefore not enough data to power this assessment. It was therefore decided, following discussion with the Trial Steering Committee, that it would not be appropriate to ask the 26 participants to undergo another cardiac MRI at week 104. The protocol has been updated to indicate that the sub-study was undertaken but was terminated due to poor recruitment, and that participants in the sub-study are not required to undergo a cardiac MRI at week 104. 2. To add a secondary endpoint to assess white matter volume (WMV) at 2 years. This involves no change to the study from a patient perspective, but rather a further analysis of the 3T scans from the study already taken for other assessments. The expertise to allow this was not available when the study started but can now be undertaken by a team member. Clarification of review of study images The study personnel involved in review of the various study images has been clarified, and Dr David Dickie added as a key collaborator. Non-substantial amendments to the study protocol Additional administrative changes and clarifications have been made as listed in the Summary of Protocol Changes document
31 July 2019	AM28 (Substantial) The secondary endpoint 'to establish whether allopurinol reduces LVH after ischaemic stroke' has been removed and a secondary endpoint of 'assess white matter volume (WMV) at 2 years has been added.
18 March 2020	AM29 (Substantial) The window for the week 104 visit has been modified, this visit can be carried out up to 3 months prior to scheduled visit or up to 6 months after the scheduled visit. The IMP can also be extended for a maximum of 6 months until the week 104 visit can be conducted. These measures will be implemented due to the restrictions imposed to combat the COVID19 pandemic. A patient letter has also been drafted to make patients aware of what will happen whilst continuing on the study.
08 April 2020	AM30 (Non-Substantial) The protocol has been update to clarify the dispensing period during the additional 6 months treatment. Patients will be dispensed a 3 month supply at week 104 and again at week 116.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported