Clinical trial results:
A phase II multicenter pilot study of the safety and efficacy of Doxycycline/UrsoDeoxyCholicAcid on disease progression in ATTR amyloidosis

Summary

EudraCT number	2011-005236-25
Trial protocol	SE
Global end of trial date	16 June 2015

Results information

Result version number	v1 (current)
This version publication date	02 February 2017
First version publication date	02 February 2017
Summary attachment (see zip file)	DoxUrso - Clinical Study report - Assessment of Safety (Clinical Study Report_DoxUrso_EudraCT 2011-005236-25_Final.pdf)

Trial information

Trial identification

Sponsor protocol code	Dox/Urso

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02016365
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Umeå University
Sponsor organisation address	Dept of Clinical Medicine and Public Health, Umeå, Sweden, 90187
Public contact	Ole B Suhr, Umeå University Dept of Clinical Medicine and Public Health, 0046 907851383, ole.suhr@medicin.umu.se
Scientific contact	Ole B Suhr, Umeå University Dept of Clinical Medicine and Public Health, 0046 907851383, ole.suhr@medicin.umu.se

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	04 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2015
Global end of trial reached?	Yes
Global end of trial date	16 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to evaluate the efficacy of doxycycline + ursodeoxycholic acid (UDCA) on disease progression in Transthyretin Amyloidosis (ATTR) subjects with cardiomyopathy with or without neuropathy.

Protection of trial subjects:

The safety profile of doxycycline + ursodeoxycholic acid (UDCA) will be assessed through the recording, reporting and analysis of baseline medical conditions, physical examination findings including vital signs and laboratory tests. Monthly phone contacts will be performed for monitoring of the treatment safety. To assess the tolerability and safety of the treatment, blood work [e.g.complete blood count, creatinine and aspartate transaminase (AST), alkaline phosphatase(ALT)] for potential drug-related adverse events will be drawn at 1, 3, 6, 9, 12 and 18 month.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	4
From 65 to 84 years	24

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects which fulfills the inclusions criteria for the study:
Adult males or non-pregnant, non-lactating females with ATTR amyloidosis, presenting cardiomyopathy with or without peripheral or autonomic neuropathy, having or not received a liver transplant 6-month prior to study entry.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Variables	N (%)	Median (Range)
Age, years		72 (56-82)
Male gender	20 (69)	
Hereditary ATTR	27 (96)	
Duration of disease (months)		24 (6-96)
PNS involvement	26 (93)	
Kumamoto score		24 (0-59)
Heart involvement	28 (100)	
LVW thickness, mm		19 (12-29)
NTproBNP ng/l		2306 (326-34678)
mBMI		947 (490-1447)

Arm type	Experimental
Investigational medicinal product name	Ursodeoxycholic acid
Investigational medicinal product code	
Other name	Ursofalk
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

750 mg/day (500 mg +250mg orally) continuously.

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

Dosage and administration details:

200 mg/day (100 mg twice daily, orally) for 4 weeks with a pause of 2 weeks.

Number of subjects in period 1	Baseline
Started	28
Completed	28

Period 2	
Period 2 title	Overall period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Doxycycline and UDCA

Arm description:

12 months of treatment with Doxycycline (200 mg/day intermittently) and UDCA (750 mg/day continuously) followed by 6 months of a withdrawal period.

Arm type	Experimental
Investigational medicinal product name	Ursodeoxycholic acid
Investigational medicinal product code	
Other name	Ursofalk
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

750 mg/day (500 mg +250mg orally) continuously.

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

Dosage and administration details:

200 mg/day (100 mg twice daily, orally) for 4 weeks with a pause of 2 weeks.

Number of subjects in period 2	Doxycycline and UDCA
Started	28
Completed	5
Not completed	23
Adverse event, serious fatal	3
Physician decision	2
Consent withdrawn by subject	6
Adverse event, non-fatal	6

Lost to follow-up	6

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	

Variables	N (%)	Median (Range)
Age, years		72 (56-82)
Male gender	20 (69)	
Hereditary ATTR	27 (96)	
Duration of disease (months)		24 (6-96)
PNS involvement	26 (93)	
Kumamoto score		24 (0-59)
Heart involvement	28 (100)	
LVW thickness, mm		19 (12-29)
NTproBNP ng/l		2306 (326-34678)
mBMI		947 (490-1447)

Reporting group values	Baseline	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	24	24	
85 years and over	0	0	
Age continuous Units: years			
median	72		
full range (min-max)	56 to 82	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	20	20	

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

Variables	N (%)	Median (Range)
Age, years		72 (56-82)
Male gender	20 (69)	
Hereditary ATTR	27 (96)	
Duration of disease (months)		24 (6-96)
PNS involvement	26 (93)	
Kumamoto score		24 (0-59)
Heart involvement	28 (100)	
LVW thickness, mm		19 (12-29)
NTproBNP ng/l		2306 (326-34678)
mBMI		947 (490-1447)

Reporting group title	Doxycycline and UDCA

Reporting group description:

12 months of treatment with Doxycycline (200 mg/day intermittently) and UDCA (750 mg/day continuously) followed by 6 months of a withdrawal period.

Subject analysis set title	Analysis for NT-pro BNP
Subject analysis set type	Per protocol

Subject analysis set description:

Analysis for NT-pro BNP

Primary: The efficacy on serum N terminal proBNP (NT-proBNP)

End point title	The efficacy on serum N terminal proBNP (NT-proBNP)

End point description:

The efficacy on serum N terminal proBNP (NT-proBNP) [Time Frame: At 12 month treatment] [Designated as safety issue: No]
The primary endpoint of the study is the response rate to doxycycline + UDCA treatment at month 12. A responder is an ATTR subject with:
- a reduction of, or an increase in serum NT-proBNP concentration of less than 30% of pre-treatment level will be regarded as consistent with treatment efficacy

End point type	Primary

End point timeframe:

At end of study period, 18 month

End point values	Baseline	Doxycycline and UDCA	Analysis for NT-pro BNP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28	5	5	
Units: NT proBNP>300 ng/L (at inclusion)				
number (not applicable)	28	5	5	

Attachments (see zip file)	Outcome of proBNP levels/Figure 1. Outcome of proBNP levels.

Statistical analyses

Statistical analysis title	Analysis for NT-proBNP
Comparison groups	Baseline v Doxycycline and UDCA
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: mBMI reduction

End point title	mBMI reduction

End point description:

End point type	Secondary

End point timeframe:

12 month

Statistical analyses

No statistical analyses for this end point

Secondary: Increase of septum thickness

End point title	Increase of septum thickness

End point description:

End point type	Secondary

End point timeframe:

At end of study period, 18 month

Statistical analyses

No statistical analyses for this end point

Secondary: Neurologic Kumamoto Scale

End point title	Neurologic Kumamoto Scale

End point description:

End point type	Secondary

End point timeframe:

At end of study period, 18 month

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability and safety of the treatment

End point title	Tolerability and safety of the treatment

End point description:

Assesment of the tolerability and safety of the treatment, i.e. monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), and the regularly scheduled monitoring of hematology, blood chemistry, physical examinations, and blood pressure over 12 months and 18 months.

End point type	Secondary

End point timeframe:

At end of study period, 18 month

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are registered from the time point when the study participants sign the informed consent until their last visit at 18 month.

Assessment type	Systematic

Dictionary used

Dictionary name	CTC AE
Dictionary version	4.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fracture rib			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hematoma			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart failure			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Heart failure aggrevated			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death NOS			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulceration			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder - other, vertebral compression			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations - other, chills			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 28 (89.29%)		
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac disorders - other, right bundel branch block			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Syncope			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Edema limbs			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions - other, thirst			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

Constipation subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5		
Dry mouth subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Dysphagia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Gastroesophageal reflux subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Hernia inguinal subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Nausea subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 7		
Stomach pain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Tooth discoloration subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Skin and subcutaneous tissue disorders			

Photosensitivity			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Skin and subcutaneous tissue - other blisters			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Urinary frequency			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Urine discolouration			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders - other, muscle cramps			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders - other, stiffness hand			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Infections and infestations			
Infection and infestations - other cold			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Infection viral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Mucosal infection mouth			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	2		
Wound infection			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		

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? No

Limitations and caveats

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

The study has extreme high drop out rate that was caused by treatment failure, side effects and voluntary dropouts, which may indicate lack of efficacy of the treatment.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28042702