Clinical trial results:
THE EFFECT OF DIFLUNISAL ON FAMILIAL TRANSTHYRETIN AMYLOIDOSIS:
An open label extension study of ”the diflunisal trial” (IND 68092), and an open label observational study on previously untreated patients with familial transthyretin amyloidosis.

Summary

EudraCT number	2011-000776-34
Trial protocol	SE
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	02 June 2019
First version publication date	02 June 2019

Trial information

Trial identification

Sponsor protocol code	DFNS01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Umea University
Sponsor organisation address	Department of Medicine and Public health, Umea, Sweden,
Public contact	Ole B Suhr, Department of Medicine and Public Health, Umea University, ole.suhr@umu.se
Scientific contact	Ole B Suhr, Department of Medicine and Public Health, Umea University, ole.suhr@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	05 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To follow the development of neurological, nutritional and cardiac manifestations of transthyretin amyloidosis in patients treated by Diflunisal 250 mg twice daily.

Protection of trial subjects:

Safety follow-up:
At 1, 3, 6, 9, 12 months and thereafter every 6 months blood samples were analysed for: B-Hb, blood platelets, s-creatinine, liver enzymes (ASAT and ALAT, s-bilirubin and ALP), S-proBNP.
Yearly neurological examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2011
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	18
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 54 patients were included at three sites; Umeå, Piteå and Skellefteå hospitals. The study population was patients with transthyretin amyloidosis.

Pre-assignment

Screening details:

Inclusion criteria:
- biopsy and genetically proven systemic transthyretin amyloidosis caused by a TTR gene mutation. The amyloid shall be proven to be of transthyretin type and the fibril composition settled.
- age 18 years and above.
- negative pregnancy test and contraception for sexually active women of childbearing potential.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	24 months treatment with Diflunisal

Arm description:

500 mg per os, Daily.

Arm type	Experimental
Investigational medicinal product name	Diflunisal
Investigational medicinal product code	ATC code N02BA11, CAS no 22494-42-4
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg per os daily

Number of subjects in period 1	24 months treatment with Diflunisal
Started	54
Completed	17
Not completed	37
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Physician decision	2
Adverse event, non-fatal	6
Liver transplant	9
Lost to follow-up	1
Change to other treatment	1
Study closure	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	54	54	
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)	18	18	
From 65-84 years	36	36	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	14	14	
Male	40	40	

End points

End points reporting groups

Reporting group title	24 months treatment with Diflunisal
Reporting group description: 500 mg per os, Daily.	
Subject analysis set title	18 months treatment with Diflunisal
Subject analysis set type	Sub-group analysis
Subject analysis set description: The 24 patients (out of 54) that completed 18 months treatment.	
Subject analysis set title	12 months treatment with Diflunisal
Subject analysis set type	Sub-group analysis
Subject analysis set description: The 34 patients (out of 54) that completed 12 months of treatment.	

Primary: Changes in the Kumamoto scale

End point title	Changes in the Kumamoto scale[1]
End point description:	
End point type	Primary
End point timeframe: After 12, 18 and 24 months treatment.	

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: There is no comparison between treatment groups.

Non-parametric statistical methods were used and p-values <0.05 were considered statistically significant.

End point values	24 months treatment with Diflunisal	18 months treatment with Diflunisal	12 months treatment with Diflunisal	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	24	34	
Units: score	17	24	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in nutritional status

End point title	Changes in nutritional status
End point description:	
End point type	Secondary
End point timeframe: After 12, 18 and 24 months of treatment.	

End point values	24 months treatment with Diflunisal	18 months treatment with Diflunisal	12 months treatment with Diflunisal	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	24	34	
Units: mBMI				
number (not applicable)	17	24	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Neurological impairment

End point title	Neurological impairment

End point description:

End point type	Secondary

End point timeframe:

After 12, 18, 24 months of treatment.

End point values	24 months treatment with Diflunisal	18 months treatment with Diflunisal	12 months treatment with Diflunisal	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	24	34	
Units: PND score	17	24	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiac impairment

End point title	Cardiac impairment

End point description:

Measured by ECG measurements of septal thickness and by proBNP in blood samples.

End point type	Secondary

End point timeframe:

After 12, 18 and 24 months of treatment.

End point values	24 months treatment with Diflunisal	18 months treatment with Diflunisal	12 months treatment with Diflunisal	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	24	34	
Units: unit	17	24	34	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Duration of the study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0
Reporting groups	
Reporting group title	Treatment with Diflunisal
Reporting group description:	
500 mg per os, Daily.	

Serious adverse events	Treatment with Diflunisal		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 54 (20.37%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorder - other, AV-block III			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder - other, absence attack				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Malnutrition				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis perforated				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrotising fasciitis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)		
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	Treatment with Diflunisal		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 54 (59.26%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Baker's cyst			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Vascular disorders Thrombophlebitis subjects affected / exposed occurrences (all)	 1 / 54 (1.85%) 1		
General disorders and administration site conditions Edema limbs subjects affected / exposed occurrences (all)	 2 / 54 (3.70%) 2		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 2 / 54 (3.70%) 2 1 / 54 (1.85%) 1		
Investigations Creatinine increased subjects affected / exposed occurrences (all) Investigations - other, Weight gain subjects affected / exposed occurrences (all) Investigations - other, increase in transaminase subjects affected / exposed occurrences (all)	 5 / 54 (9.26%) 5 1 / 54 (1.85%) 1 1 / 54 (1.85%) 2		
Injury, poisoning and procedural complications Fibula fracture subjects affected / exposed occurrences (all)	 1 / 54 (1.85%) 1		
Cardiac disorders Cardiac disorders - other, Increased pro-BNP subjects affected / exposed occurrences (all) Cardiac disorder - other, irregular heart rate	 1 / 54 (1.85%) 1		

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomach pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Gastrointesinal disorder - other, blood in stool			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Fecal incontinence			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Heartburn			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema scaling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Nail fragile			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hair loss			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Infections and infestations - other, infected abrasion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cold			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Salmonella			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infections and infestations- other,			

Shingles			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 54 (1.85%)		
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 was closed due to publication of the Diflunisal study by Berk et. al., JAMA, Dec 2013.

Notes: