Clinical trial results:
THE EFFECT OF DIFLUNISAL ON FAMILIAL TRANSTHYRETIN AMYLOIDOSIS:
An open label phase III extension study of the diflunisal trials (IND 68092 and DFNS01), and an open label observational study on previously untreated patients with familial transthyretin amyloidosis complicated by cardiomyopathy.

Summary

EudraCT number	2014-001957-17
Trial protocol	SE
Global end of trial date	04 June 2021

Results information

Result version number	v1 (current)
This version publication date	30 June 2022
First version publication date	30 June 2022

Trial information

Trial identification

Sponsor protocol code	DFNS02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Umeå University Hospital
Sponsor organisation address	Norrlands universitetssjukhus, Umeå, Sweden,
Public contact	Intissar Anan, Umeå University Hospital, 46 9078550000, intissar.anan@umu.se
Scientific contact	Intissar Anan, Umeå University Hospital, 46 9078550000, intissar.anan@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	16 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2021
Global end of trial reached?	Yes
Global end of trial date	04 June 2021
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.
Primary end-points
1. changes in the Kumamoto scale
2. cardiac impairment measured by echocardiographic assessment of global systolic strain

Protection of trial subjects:

The patient was safety evaluated 1 month, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months. Blood samples: B-Hb, B- platelets, s-creatinine, liver enzymes (ASAT and ALAT, s- bilirubin and ALP). S- pro-BNP and Troponin. Detection and documentation of any events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE).

Clinically significant AEs considered by the investigator to be related to treatment were followed until resolved or considered stable. It was left to the investigator's clinical judgment to determine whether an AE was related and of sufficient severity to require the subject's removal from treatment or from the trial. A subject was also able to voluntarily withdraw from treatment due to what he or she perceived as an intolerable AE.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	6
From 65 to 84 years	25
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 32 patients were included at two sites, Umeå and Piteå. Study population was patient with transthyretin amyloidosis.

Pre-assignment

Screening details:

Patients who have participated in the DFNS01-study were asked to participate in this extensional study. New patients, who fulfilled the eligibility criteria were enrolled as well.

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 of treatment with Diflunisal
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Diflunisal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg x 2 p.o

Number of subjects in period 1	24 months of treatment with Diflunisal
Started	32
Completed	19
Not completed	13
Due to pandemic, did not come to study visit	2
Patients wish, did not come to study visits	1
Did not take study drug	1
Adverse event, non-fatal	4
Due to licence problem, no study drug	3
Did not fulfill inclusion criteria	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
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)	6	6	
From 65-84 years	25	25	
85 years and over	1	1	
Not recorded	0	0	
Gender categorical Units: Subjects			
Female	11	11	
Male	21	21	

End points

End points reporting groups

Reporting group title	24 months of treatment with Diflunisal
Reporting group description: -	
Subject analysis set title	12 months treatment with Diflunisal
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Primary endpoints measured at 12 months and 24 months of treatment with Diflunisal	

Primary: Changes in the Kumamoto scale

End point title	Changes in the Kumamoto scale
End point description:	
End point type	Primary
End point timeframe:	
Primary end-points will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.	

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	27		
Units: Scale unit				
number (not applicable)	32	32		

Statistical analyses

Statistical analysis title	Descriptive statistics
Statistical analysis description:	
Changes over time for primary end-points will be analysed by one-way ANOVA to detect significant changes over time.	
Comparison groups	24 months of treatment with Diflunisal v 12 months treatment with Diflunisal
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Kumamoto scale is measured at 0 month, 12 month and 24 months. Same subjects but different time frames.

Primary: Cardiac impairment measured by echocardiographic assessment of global systolic strain

End point title	Cardiac impairment measured by echocardiographic

	assessment of global systolic strain

End point description:

End point type	Primary

End point timeframe:

Primary end-points will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	27		
Units: Percent	32	32		

Statistical analyses

Statistical analysis title	Descriptive statistics

Statistical analysis description:

Changes over time for primary- and secondary end-points will be analysed by one-way ANOVA to detect significant changes over time.

Comparison groups	24 months of treatment with Diflunisal v 12 months treatment with Diflunisal
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Same subjects but different time frames.

Secondary: Changes in nutritional status measured by the modified body mass index

End point title	Changes in nutritional status measured by the modified body mass index

End point description:

End point type	Secondary

End point timeframe:

Secondary end-point will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	26		
Units: mBMI	32	32		

Statistical analyses

No statistical analyses for this end point

Secondary: changes in neurological impairment measured by the PND-score

End point title	changes in neurological impairment measured by the PND-score

End point description:

End point type	Secondary

End point timeframe:

Secondary end-point will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	26		
Units: PND-score				
number (not applicable)	32	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiac impairment, echocardiographic measurement of septal thickness and blood pro-BNP concentration

End point title	Cardiac impairment, echocardiographic measurement of septal thickness and blood pro-BNP concentration

End point description:

End point type	Secondary

End point timeframe:

Secondary end-point will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	27	25		
Units: Mass/Vol	32	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Karnofsky performance scale

End point title	Karnofsky performance scale

End point description:

End point type	Secondary

End point timeframe:

Secondary end-points will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	26		
Units: KPS				
number (not applicable)	32	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Drug safety

End point title	Drug safety

End point description:

End point type	Secondary

End point timeframe:

Secondary end-point will be evaluated at 12 months and the end of the 24 months study period by descriptive statistical methods.

End point values	24 months of treatment with Diflunisal	12 months treatment with Diflunisal		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	29		
Units: Number of	32	32		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study from the time of subject's signature of informed consent.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Adverse Event

Reporting group description:

An adverse event is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline (i.e. present at the initial study visit) during a clinical study with an Investigational Medicinal Product, regardless of causal relationship and even if no Investigational Medicinal Product has been administered.

Serious adverse events	Adverse Event		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ankle fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
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	Adverse Event		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 30 (76.67%)		
Vascular disorders			
Hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Dehydration			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Polyneuropathy			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
General disorders and administration site conditions,other; Cold feet, discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Snoring			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pneumothorax			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fracture			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Edema			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		

Dyspnea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Frontotemporal dementia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Parkinson's disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Eye disorders			
cataract surgery			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vitreous opacities			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vitreous hemorrhage			

alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastritis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Dyspepsia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Liver function test increased			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Eczema	Additional description: Eczema		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin lesion			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Creatinine renal clearance decreased			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Urinary retention	Additional description: Urinary retention		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Systematic			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Infections and infestations			
Sinuitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2018	Prolongation of the study with 2 years.

Notes:

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.

Due to regulatory issue with licence with study medication there were several patients that could not fulfill the study.

Notes: