Clinical Study Report – Assessment of Safety

Study title:

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

EudraCT number:
2011-005236-25

Study drug:

Doxycycline
Ursodeoxycholic acid

Report period:
2012 02 06 – 2015 06 16

Report date:
2016 08 30

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TABLE OF CONTENT

SUMMARY AND COMMENTS 4
1. INTRODUCTION 4
2. WORLDWIDE MARKETING APPROVAL STATUS 4
3. ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS 5
3.1 STUDY DISCONTINUATION 5
3.2 STUDY DRUG DISCONTINUED 5
3.2.1 Listing of adverse events which resulted in a discontinuation of study medication 5
4. CHANGES TO REFERENCE SAFETY INFORMATION 5
5. INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD 6
6. ESTIMATED CUMULATIVE EXPOSURE 6
6.1 CUMULATIVE SUBJECT EXPOSURE IN THE DEVELOPMENT PROGRAMME 6
6.2 PATIENT EXPOSURE FROM MARKETING EXPERIENCE 6
7. CUMULATIVE SUMMARY TABULATIONS 6
7.1 REFERENCE INFORMATION 6
7.2 CUMULATIVE LISTINGS OF SERIOUS ADVERSE REACTIONS DURING THE REPORTING PERIOD 6
7.3 CUMULATIVE AE (NON SERIOUS) WITH CAUSALITY RELATED 9
7.4 CUMULATIVE AE (NON SERIOUS) WITH CAUSALITY NOT RELATED 9
7.5 CUMULATIVE AE NUMBER OBSERVED AND RATE WITH PATIENT IDENTIFICATIONS 9
8. SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD 9
8.1 COMPLETED CLINICAL TRIALS 9
8.2 ONGOING CLINICAL TRIALS 9
8.3 LONG-TERM FOLLOW-UP 9
8.4 OTHER THERAPEUTIC USE OF INVESTIGATIONAL DRUG 9
8.5 NEW SAFETY DATA RELATED TO COMBINATION THERAPIES 9
9. SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES 9
10. OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION 10
11. SAFETY FINDINGS FROM MARKETING EXPERIENCE 10
12. NON-CLINICAL DATA 10
13. LITERATURE 10
14. OTHER DSURS 10
15. LACK OF EFFICACY 10
16. REGION-SPECIFIC INFORMATION 10
17. LATE-BREAKING INFORMATION 10
18. OVERALL SAFETY ASSESSMENT 10
18.1 EVALUATION OF THE RISKS 10
18.2 BENEFIT-RISK CONSIDERATION 10
19. SUMMARY OF IMPORTANT RISKS 11

20. CONCLUSIONS **11**
APPENDIX I **12**
APPENDIX II **13**
APPENDIX III **14**
APPENDIX IV **18**
APPENDIX V **18**

Summary and comments

The main purpose of the study was to study the safety, efficacy and to explore the potential benefits of a twelve-month treatment with Doxycycline combined with UrsoDeoxyCholicAcid (UDCA) on disease progression in Transthyretin Amyloidosis (ATTR) patients.

The primary endpoint of the study was 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.

The heart function was evaluated by measuring of NT-proBNP, and septal thickness. For inclusion a septal thickness above 15 mm and/or a NT pro BNP above 300 ng/L was used.

Secondary endpoints of the study were:
-mBMI-reduction of less than 10% after 12 months of treatment
- increase of septum thickness ≤ 2 mm during 12 months of treatment.
- to assess the change from baseline in the neurologic Kumamoto Scale at months 6, 12 and 18;
- to assess 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.

1. Introduction

The study population consisted of ATTR subjects with cardiomyopathy with or without neuropathy including patients having performed a liver transplantation more than 6 months before entry. The patients were recruited at Norrlands University Hospital in Umeå, the Hospital in Skellefteå and at the Hospital in Piteå.

All eligible ATTR subjects received doxycycline as Doxyferm® 200 mg/day (100 mg twice daily, orally) for 4 weeks with a pause of 2 weeks in combination with UDCA as Ursofalk® 750 mg/day (500 mg +250mg orally) continuously. Treatment was administered for 12 months followed by a withdrawal period where the patients were monitorered for disease progression and safety.

A total of 28 patients were enrolled in the study. The study started to include patients 2012 02 06 (first subject first visit) and ended 2015 06 16 (last subject last visit).

2. Worldwide Marketing Approval Status

Not applicable in this investigator initiated clinical trial.

3. Actions Taken in the Reporting Period for Safety Reasons

Adverse Events have been followed for all patients enrolled in the study and reported in accordance with current regulations and approved protocol.

3.1 Study discontinuation

23 patients, out of 28, did not complete the study. The reasons were the following: three patient died before the last date of the study, five patients did not come to the planned study visits, five patients discontinued due to adverse event, one patient discontinued due to a combination of adverse event and missing study visits, two patients discontinued due to treatment failure, one patient discontinued due to other unknown reason and six patients discontinued due to withdrawal of the consent.

3.2 Study drug discontinued

3.2.1 Listing of adverse events which resulted in a discontinuation of study medication

Patient number/ id	Study drug	Adverse Event	SAE	Causality assessment
UM01	Doxycycline / UrsoDeoxyCholicAcid	Nausea	No	Yes
UM09	Doxycycline / UrsoDeoxyCholicAcid	Constipation Edema limbs Musculoskeletal and connective tissue disorders - other, muscle cramps and stiffness hand	No No No No	Yes Yes Yes Yes
Pi01	Doxycycline / UrsoDeoxyCholicAcid	Sudden death NOS	Yes	No
Pi02	Doxycycline / UrsoDeoxyCholicAcid	Heart failure	Yes	No
Pi05	Doxycycline / UrsoDeoxyCholicAcid	Rash Paraesthesia	No No	Yes Rash No Paraesthesia
Pi08	Doxycycline / UrsoDeoxyCholicAcid	Skin and subcutaneous tissue, other blisters	No	Yes
SK01	Doxycycline / UrsoDeoxyCholicAcid	Pruritus	No	No
SK02	Doxycycline / UrsoDeoxyCholicAcid	Skin ulceration	Yes	Yes

4. Changes to Reference Safety Information

Not applicable when it is an investigator initiated clinical trial.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

Not applicable.

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme

Not applicable.

6.2 Patient Exposure from Marketing Experience

Not applicable.

7. Cumulative Summary Tabulations

7.1 Reference Information

Latest in Sweden approved summary of product characteristics for Doxyferm (Doxycycline), appendix IV (detached), and Ursofalk (UrsoDeoxyCholicAcid), appendix V (detached).

7.2 Cumulative Listings of Serious Adverse Reactions during the Reporting Period

Reporting period: 2012 02 06 – 2015 06 16.

15 Serious Adverse Events, no SUSAR, have occurred in this study during the reporting period.

Study medication was discontinued due to one SAE, Skin ulceration, and in two events, with Cardiac failure, the study medication had already been discontinued before the SAE occurred.

	Patient number	**Study drug**	**Adverse Event** CTC AE	**SAE**	**Causality assessment**
1	UM07	Doxycycline / UrsoDeoxyCholicAcid	Hematoma	Yes	Unlikely
2	UM10	Doxycycline / UrsoDeoxyCholicAcid	Dyspnoea	Yes	Unrelated
3	UM10	Doxycycline / UrsoDeoxyCholicAcid	Musculoskeletal and connective tissue disorder - other, vertebral compression	Yes	Unrelated
4	UM13	Doxycycline / UrsoDeoxyCholicAcid	Heart failure aggravated	Yes	No
5	UM14	Doxycycline / UrsoDeoxyCholicAcid	Vertigo	Yes	Unlikely

	Patient number	Study drug	Adverse Event CTC AE	SAE	Causality assessment
6	Pi01	Doxycycline / UrsoDeoxyCholicAcid	Sudden death NOS	Yes	No
7	Pi02	Doxycycline / UrsoDeoxyCholicAcid Studymedication was discontinued before the SAE occurred.	Heart failure	Yes	No
8	Pi04	Doxycycline / UrsoDeoxyCholicAcid	Sepsis	Yes	No
9	Pi04	Doxycycline / UrsoDeoxyCholicAcid	Infections and infestations - other, chills	Yes	No
10	Pi05	Doxycycline / UrsoDeoxyCholicAcid	Wrist fracture	Yes	No
11	Pi07	Doxycycline / UrsoDeoxyCholicAcid	Stroke	Yes	No
12	Pi07	Doxycycline / UrsoDeoxyCholicAcid	Diarrhoea	Yes	Yes
13	Pi09	Doxycycline / UrsoDeoxyCholicAcid	Fracture rib	Yes	No
14	SK02	Doxycycline / UrsoDeoxyCholicAcid	Skin ulceration	Yes	Yes
15	SK04	Doxycycline / UrsoDeoxyCholicAcid Studymedication was discontinued before the SAE occurred.	Heart failure	Yes	Unrelated

1. SAE Hematoma.
The patient experienced intramuscular bleeding, left thigh, due to waran treatment and was hospitalised. The patient recovered and causality was assessed as unlikely related to the study medication. The treatment with study medication continued unchanged.

2. SAE Dyspnoea.
The patient was hospitalised due to dyspnoea and recovered two days later. Causality was assessed as unrelated to the study medication. The treatment with study medication continued unchanged.

3. SAE Musculoskeletal and connective tissue disorder - other, vertebral compression.
The patient was hospitalised due to vertebral compression. Causality was assessed as unrelated to the study medication. The treatment with study medication continued without changes.

4. SAE Heart failure aggrevated.

Causality was assessed as not related to the study medication. The treatment with study medication continued unchanged.

5. SAE Vertigo. The patient was hospitalised due to vertigo. Two days later the patients recovered and causality was assessed as not related to the study medication. The treatment with study medication continued unchanged.

6. SAE Sudden death NOS.
The patient had a known medical history of FAP (Familial Amyloidotic Polyneuropathy), urinary retention and chronic ischemic heart disease. Had no deterioration of his heart symptoms or FAP symptoms when he suddenly died. Cause of death is not known. Causality was assessed as not related to the study medication.

7. SAE Heart failure.
The patient died and cause of death was FAP (Familial Amyloidotic Polyneuropathy). The treatment with study medication had been stopped three months before the death and causality was assessed as not related to the study medication.

8. SAE Sepsis.
The patient was hospitalised due to sepsis. Ten days later the patient recovered and causality was assessed as not related to the study medication. The treatment with study medication continued unchanged.

9. SAE Infections and infestations other-chills.
The patient was hospitalised due to chills, an infection was suspected. Four days later the patient recovered and causality was assessed as not related to the study medication. The treatment with study medication continued unchanged.

10. SAE Wrist fracture.
The patient had a wrist fracture and was hospitalised. Causality was assessed as not related to the study medication. The treatment with study medication continued and the patient recovered after almost 2 months.

11. SAE Stroke.
The patient had a stroke and was hospitalised. Causality was assessed as not related to the study medication. The treatment with study medication continued. The patient recovered with sequelae.

12. SAE Diarrhoea.
The patient suffered from diarrhoea with dehydration for 3-4 days and was hospitalised. Causality was assessed as related to the study medication. The treatment with study medication continued unchanged.

13. SAE Fracture rib.
The patient fell and suffered from a rib fracture. Causality was assessed as not related to the study medication. The treatment with study medication had already been stopped 3 weeks before according to the study protocol.

14. SAE Skin ulceration.
The patient got ulcer on his hands for approximately 2 weeks. Causality was assessed as related to the study medication and the patient recovered when he stopped the treatment with Doxycycline. The treatment with UrsoDeoxyCholicAcid continued unchanged.

15. SAE Heart failure.
The patient died due to heart failure. The treatment with study medication was stopped four months before the patient died. The causality was assessed as unrelated to study medication.

7.3 Cumulative AE (non serious) with causality related

Non-serious AE evaluated to be related to study drug were primarily of gastro intestinal discomfort type, skin/photosensitivity reactions or oedema.
See appendix I.

7.4 Cumulative AE (non serious) with causality not related

Non-serious AE evaluated not to be related to study drug appeared to conform well to the general patient population.
See appendix II.

7.5 Cumulative AE Number Observed and Rate with patient identifications

Gastrointestinal disorders constituted the largest number of AE (i.e. nausea and diarrhoea) followed by Skin and subcutaneous tissue disorders (AE i.e. photosensitivity and rash). It appears not deviating from what is expected with the treatment.
See appendix III.

8. Significant Findings from Clinical Trials during the Reporting Period

Not applicable in an investigator initiated study.

8.1 Completed Clinical Trials

Not applicable.

8.2 Ongoing Clinical Trials

Not applicable.

8.3 Long-term Follow-up

Not applicable.

8.4 Other Therapeutic Use of Investigational Drug

Not applicable.

8.5 New Safety Data Related to Combination Therapies

Not applicable.

9. Safety Findings from Non-interventional Studies

Not applicable.

10. Other Clinical Trial/Study Safety Information

Not applicable.

11. Safety Findings from Marketing Experience

Not applicable.

12. Non-clinical Data

Not applicable.

13. Literature

Not applicable.

14. Other DSURs

No previous DSUR.

15. Lack of Efficacy

Two patients discontinued with study medication due to treatment failure (Patient UM12 and UM16).

16. Region-Specific Information

Not applicable.

17. Late-Breaking Information

Not applicable.

18. Overall Safety Assessment

Generally, the drug was well tolerated. The side effects were those expected with Doxycyclin and UrsoDeoxyCholicAcid. Discontinuation of the drug due to a SAE included skin ulceration, a rare but possible side effect of Doxycyclin treatment. One patient died suddenly. However, sudden death is not uncommon in patients suffering from amyloid cardiomyopathy, and in addition, the patient had also an ischemic heart disease, so we regard this event as unrelated to the study drugs.

Skin rash and photosensibility is reported with a frequency of between 1/100-1/1000 and is a known side effect of Doxycycline.

18.1 Evaluation of the Risks

Considering the patient population, with a severe progressive systemic amyloidosis, the side effects were acceptable.

18.2 Benefit-risk Consideration

No Double blind trial of Doxycycline/Ursodeoxycholic acid has been reported. However, from Italy, an open-label study has reported beneficial effects of the combination of Doxycycline and Tauro-deoxy-cholic acid treatment (Obici Let al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. Amyloid. 2012;19 Suppl 1:34-6). Considering the serious prognosis of TTR-amyloid cardiomyopathy, the benefit associated with treatment by the investgational drugs outweights in our opinion the risks.

19. Summary of Important Risks

The study population consisted of patients suffering from ATTR-amyloidosis with cardiomyopathy and heart failure. The side effects reported for doxycycline, such as nausea/vomiting and diarrhoea, are also known symptoms of ATTR amyloidosis. Skin ulcerations was the only important risk factor that was related to a SAE and that lead to sudy discontinuation.

20. Conclusions

The combination of Doxtcycline and Ursodeoxy-cholic-acid appears to be well tolerated by patients suffering from systemic ATTR amyloidosis with amyloid cardiomyopathy. No unexpected side effects were disclosed in the present study.

Appendix I

Cumulative AE (non serious) with causality related

Patient number	Study drug	Adverse Event CTC AE	SAE	Causality assessment
UM01		Nausea	No	Yes
UM02		Nausea	No	Yes
UM02		Nausea	No	Yes
UM02		Mucosal infection mouth	No	Yes
UM02		Mucosal infection mouth	No	Yes
UM03		Flushing	No	Yes
UM05		Nausea	No	Yes
UM07		Nausea	No	Yes
UM07		Photosensitivity	No	Yes
UM08		Photosensitivity	No	Yes
UM08		Diarrhoea	No	Yes
UM09		Musculoskeletal and connective tissue disorders - other, muscle cramps	No	Yes
UM09		Edema limbs	No	Yes
UM09		Constipation	No	Yes
UM09		Musculoskeletal and connective tissue disorders - other, stiffness hand	No	Yes
UM10		Stomach pain	No	Yes
UM11		Photosensitivity	No	Yes
UM12		Photosensitivity	No	Yes
UM02		Nausea	No	Possible
UM02		Vomiting	No	Possible
UM02		Diarrhoea	No	Possible
UM08		Stomach pain	No	Possible
UM08		Edema limbs	No	Possible
UM08		Dyspnoea	No	Possible
Pi05		Rash	No	Yes
Pi06		Photosensitivity	No	Yes
Pi07		Photosensitivity	No	Yes
Pi07		Diarrhoea	No	Yes
Pi08		Skin and subcutaneous tissue, other blisters	No	Yes
Pi10		Photosensitivity	No	Yes

Appendix II

Cumulative AE (non serious) with causality not related

Patient number	Study drug	Adverse Event	SAE	Causality assessment
UM02		Rash	No	No
UM03		Rash	No	No
UM03		Edema limbs	No	No
UM03		Wound infection	No	No
UM04		Haematuria	No	No
UM04		Nausea	No	No
UM04		Back pain	No	No
UM04		Depressed level of consciousness	No	Nej
UM05		Dysphagia	No	No
UM05		Diarrhoea	No	No
UM06		Cardiac disorders - other, right bundel branch block	No	No
UM07		Infection and infestations other: cold	No	No
UM08		Creatinine increased	No	No
UM10		Fatigue	No	No
UM11		Haematuria	No	No
UM13		Urinary tract infection	No	No
UM13		General disorders and administration site conditions - other, thirst	No	No
UM14		Paraesthesia	No	No
UM14		Vomiting	No	No
UM14		Syncope	No	No
UM14		Memory impairment	No	No
UM14		Haematuria	No	No
UM14		Oedema legs	No	No
UM14		Urinary frequency	No	No
UM14		Paraesthesia	No	No
UM14		Dry mouth	No	No
UM16		Fatigue	No	No
UM16		Tooth discoloration	No	No
Pi02		Hernia inguinal	No	No
Pi03		Infection viral	No	No
Pi05		Paraesthesia	No	No
Pi05		Abdominal pain	No	No
Pi05		Vomiting	No	No
Pi05		Diarrhoea	No	No
Pi06		Haematuria	No	No
Pi07		Paraesthesia	No	No
Pi08		Cataract	No	No
Pi08		Constipation	No	Unlikely
Pi08		Urine discolouration	No	Unlikely
Pi09		Chest pain	No	No
Pi09		Haematuria	No	No
Pi09		Gastroesophageal reflux	No	No
SK01		Pruritus	No	No
SK02		Urinary tract infection	No	No
SK02		Rash	No	No

Appendix III

Cumulative AE Number Observed and Rate with patient identifications

SOC	CTC AE	Related**	Not related***	Total cases
Cardiac disorder				
	Cardiac disorders - other, right bundel branch block		UM06*	
	Heart failure		Pi02*	
	Heart failure		SK04*	
	Heart failure aggravated		UM13*	
		Total # (%)	**4 (4.4%)**	**4 (4.4%)**
Ear and labyrinth disorders				
	Vertigo		UM14*	
		Total # (%)	**1 (1.1%)**	**1 (1.1%)**
Eye disorders				
	Cataract		Pi08*	
		Total # (%)	**1 (1.1%)**	**1 (1.1%)**
Gastrointestinal disorders				
	Abdominal pain		Pi05*	
	Constipation	UM09*		
	Constipation		Pi08*	
	Diarrhoea	UM02*		
	Diarrhoea		UM05*	
	Diarrhoea	UM08*		
	Diarrhoea		Pi05*	
	Diarrhoea	Pi07*		
	Diarrhoea	Pi07*		
	Dry mouth		UM14*	
	Dysphagia		UM05*	
	Gastroesophageal reflux		Pi09*	
	Hernia inguinal		Pi02*	
	Nausea	UM01*		
	Nausea	UM02*		
	Nausea	UM02*		
	Nausea	UM02*		
	Nausea		UM04*	
	Nausea	UM05*		
	Nausea	UM07*		
	Stomach pain	UM08*		
	Stomach pain	UM10*		

SOC	CTC AE		Related**	Not related***	Total cases
	Tooth discoloration			UM16*	
	Vomiting		UM02*		
	Vomiting			UM14*	
	Vomiting			Pi05*	
		Total # (%)	**14 (15.6%)**	**12 (13.3%)**	**26 (28.9%)**
General disorders and administration site conditions					
	Chest pain			Pi09*	
	Edema limbs			UM03*	
	Edema limbs		UM08*		
	Edema limbs		UM09*		
	Edema limbs			UM14*	
	Fatigue			UM10*	
	Fatigue			UM16*	
	General disorders and administration site conditions - other, thirst			UM13*	
	Sudden death NOS			Pi01*	
		Total # (%)	**2 (2.2%)**	**7 (7.8%)**	**9 (10.0%)**
Infections and infestations					
	Infection and infestations other: cold			UM07*	
	Infection viral			Pi03*	
	Infections and infestations - other, chills			Pi04*	
	Mucosal infection mouth		UM02*		
	Mucosal infection mouth		UM02*		
	Sepsis			Pi04*	
	Urinary tract infection			SK02*	
	Wound infection			UM03*	
		Total # (%)	**2 (2.2%)**	**6 (6.7%)**	**8 (8.9%)**
Injury, poisoning and procedural complications					
	Fracture rib			Pi09*	
	Wrist fracture			Pi05*	
		Total # (%)		**2 (2.2%)**	**2 (2.2%)**
Investigations					
	Creatinine increased			UM08*	
		Total # (%)		**1 (1.1%)**	**1 (1.1%)**

SOC	CTC AE		Related**	Not related***	Total cases
Musculoskeletal and connective tissue disorders					
	Back pain			UM04*	
	Musculoskeletal and connective tissue disorder - other, vertebral compression			UM10*	
	Musculoskeletal and connective tissue disorders - other, muscle cramps		UM09*		
	Musculoskeletal and connective tissue disorders - other, stiffness hand		UM09*		
		Total # (%)	**2 (2.2%)**	**2 (2.2%)**	**4 (4.4%)**
Nervous system disorders					
	Depressed level of consciousness			UM04*	
	Memory impairment			UM14*	
	Paraesthesia			UM14*	
	Paraesthesia			UM14*	
	Paraesthesia			Pi05*	
	Paraesthesia			Pi07*	
	Stroke			Pi07*	
	Syncope			UM14*	
		Total # (%)		**8 (8.9%)**	**8 (8.9%)**
Renal and urinary disorder					
	Haematuria			UM04*	
	Haematuria			UM11*	
	Haematuria			UM14*	
	Haematuria			Pi06*	
	Haematuria			Pi09*	
	Urinary frequency			UM14*	
	Urinary tract infection			UM13*	
	Urine discolouration			Pi08*	
		Total # (%)		**8 (8.9%)**	**8 (8.9%)**
Respiratory, thoracic and mediastinal disorders					
	Dyspnoea		UM08*		
	Dyspnoea			UM10*	
		Total # (%)	**1 (1.1%)**	**1 (1.1%)**	**2 (2.2%)**

SOC	CTC AE	Related**	Not related***	Total cases
Skin and subcutaneous tissue disorders				
	Photosensitivity	UM07*		
	Photosensitivity	UM08*		
	Photosensitivity	UM11*		
	Photosensitivity	UM12*		
	Photosensitivity	Pi06*		
	Photosensitivity	Pi07*		
	Photosensitivity	Pi10*		
	Pruritus		SK01*	
	Rash		UM02*	
	Rash		UM03*	
	Rash	Pi05*		
	Rash		SK02*	
	Skin and subcutaneous tissue, other blisters	Pi08*		
	Skin ulceration	SK02*		
	Total # (%)	**10 (11.1%)**	**4 (4.4%)**	**14 (15.5%)**
Vascular disorders				
	Flushing	UM03*		
	Hematoma		UM07*	
	Total # (%)	**1 (1.1%)**	**1 (1.1%)**	**2 (2.2%)**
	Total Events # (%)	**32 (35.6%)**	**58 (64.4%)**	**90 (100%)**

* Patient identification number
** Causal relationship to study medication Related = Assessment is Yes, Related or Possible
*** Causal relationship to study medication Not related = Assessment is No, Not related, Unlikely or Unrelated.

Appendix IV

Summary of product characteristics for Doxyferm (Doxycycline) in Swedish. Please find detached pdf (Appendix IV – Doxyferm).

Appendix V

Summary of product characteristics for Ursofalk (UrsoDeoxyCholicAcid) in Swedish. Please find detached pdf (Appendix V – Ursofalk).