Clinical experience on Captafer in Czech Republic

Captafer was tested in 16 patients suffering from anaemia due to various conditions.
Blood parameters were measured (haemoglobin, iron, ferritin, binding capacity) before and after one month treatment with Captafer.
The results are presented in Outline 1 and clearly show that in 15 of the patients, the iron level in blood was increased.

A protocol was recently submitted to an ethical committee in Brno for a study called "An Open Multicentric Pilot Study on Clinical Efficacy of Iron-Free Oral Fish Cartilage in Patients with Inflammatory Bowel Diseases suffering from Chronic Iron Deficiency Anaemia."
As soon as the ethical committee endorse the protocol, the study will start rapidly.
(cf. Attachment 2)

Outline 1: Captafer survey results in Czech Republic

	PATIENT	DISEASE	SEX	BEFORE	1 MONTH AFTER TREATMENT	RESULTS	DIFFERENCE
Č.1		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			109,00	113,00	↑	4,00
	IRON µmol/l			4,80	4,90	↑	0,10
	FERRITIN mg/ml			6,10	6,70	↑	0,50
	BONDING CAPACITY µmol/l			84,10	83,00	↓	1,10
Č.2		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			114,00	120,00	↑	6,00
	IRON µmol/l			4,94	5,20	↑	0,26
	FERRITIN mg/ml			5,60	13,00	↑	7,40
	BONDING CAPACITY µmol/l			84,10	83,10	↓	1,00
Č.3		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			102,00	101,00	↓	1,00
	IRON µmol/l			8,11	8,25	↑	0,14
	FERRITIN mg/ml			7,20	8,00	↑	0,80
	BONDING CAPACITY µmol/l			47,50	46,20	↓	1,30
Č.4		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			96,00	115,00	↑	19,00
	IRON µmol/l			3,90	8,11	↑	4,21
	FERRITIN mg/ml			5,40	7,25	↑	1,85
	BONDING CAPACITY µmol/l			87,20	67,50	↓	19,70
Č.5		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			120,00	137,00	↑	17,00
	IRON µmol/l			27,01	28,00	↑	0,99
	FERRITIN mg/ml			23,70	30,00	↑	6,30
	BONDING CAPACITY µmol/l			43,20	47,10	↑	3,90
Č.6		**GYN. ANEMIE**	**F**				
	HEMOGLOBIN g/l			119,00	125,00	↑	6,00
	IRON µmol/l			13,50	13,00	↓	0,50
	FERRITIN mg/ml			24,40	27,30	↑	2,90
	BONDING CAPACITY µmol/l			45,10	45,20	↑	0,10

Č.7		**GYN. ANEMIE**	**F**					
	HEMOGLOBIN g/l			111,00	120,00		↑	9,00
	IRON µmol/l			11,09	11,80		↑	0,71
	FERRITIN mg/ml			30,20	35,00		↑	4,80
	BONDING CAPACITY µmol/l			44,10	44,75		↑	0,65
Č.8		**CROHN**	**M**					
	HEMOGLOBIN g/l			116,00	114,00		↓	2,00
	IRON µmol/l			8,20	8,30		↑	0,10
	FERRITIN mg/ml			7,30	7,20		↓	0,10
	BONDING CAPACITY µmol/l			66,70	67,10		↑	0,40
Č.9		**GIT ANEMIE**	**F**					
	HEMOGLOBIN g/l			112,00	125,00		↑	13,00
	IRON µmol/l			11,90	13,20		↑	1,30
	FERRITIN mg/ml			24,40	28,10		↑	4,00
	BONDING CAPACITY µmol/l			48,20	45,00		↓	3,20
Č.10		**GIT ANEMIE**	**F**					
	HEMOGLOBIN g/l			126,00	136,00		↑	10,00
	IRON µmol/l			5,25	11,02		↑	5,77
	FERRITIN mg/ml			13,50	29,10		↑	15,60
	BONDING CAPACITY µmol/l			82,10	44,00		↓	38,10
Č.11		**ULC. KOLITIDA**	**F**					
	HEMOGLOBIN g/l			98,00	109,00		↑	11,00
	IRON µmol/l			3,70	4,90		↑	1,20
	FERRITIN mg/ml			5,50	6,20		↑	0,70
	BONDING CAPACITY µmol/l			86,30	83,20		↓	3,10
Č.12		**GIT ANEMIE**	**F**					
	HEMOGLOBIN g/l			106,00	120,00		↑	14,00
	IRON µmol/l			4,70	8,60		↑	3,90
	FERRITIN mg/ml			6,00	7,52		↑	1,52
	BONDING CAPACITY µmol/l			85,10	63,50		↓	21,60
Č.13		**CROHN**	**M**					
	HEMOGLOBIN g/l			102,00	104,00		↑	2,00
	IRON µmol/l			8,12	8,24		↑	0,12
	FERRITIN mg/ml			7,28	7,31		↑	0,03
	BONDING CAPACITY µmol/l			46,20	46,10		↓	0,10
Č.14		**GIT ANEMIE**	**F**					
	HEMOGLOBIN g/l			127,00	120,00	122,00	↑	7,00
	IRON µmol/l			2,70	7,60	12,00	↑	4,90
	FERRITIN mg/ml			3,20	4,60	5,90	↑	1,40
	BONDING CAPACITY µmol/l			77,10	73,30	69,10	↓	3,80
Č.15		**ULC. KOLITIDA**	**F**					
	HEMOGLOBIN g/l			93,00	102,00		↑	9,00
	IRON µmol/l			2,40	29,20		↑	
	FERRITIN mg/ml			7,00	5,00		↓	26,80
	BONDING CAPACITY µmol/l			63,60				
Č.16		**ULC. KOLITIDA**	**F**					
	HEMOGLOBIN g/l			115,00	113,00		↑	2,00
	IRON µmol/l			3,50	6,10		↑	2,60
	FERRITIN mg/ml			11,00	4,50		↓	6,50
	BONDING CAPACITY µmol/l			76,70	77,20		↑	0,50

Attachment 2:

STUDY PROTOCOL

Name of Company: Nordic, s.r.o., K Rybniku 475, 252 42 Jesenice u Prahy, Czech Republic	
Name of Finished Product: CAPTAFER ™	
Name of Active Ingredient: Fish cartilage extract	
Title of study: ***An Open Multicentric Pilot Study on Clinical Efficacy of Iron-Free Oral Fish Cartilage in Patients with Inflammatory Bowel Diseases suffering from Chronic Iron Deficiency Anaemia*** **Study code**: NO-CAPT-001	
Coordinating Investigator: prof. MUDr. Jan Lata, CSc	
Study centre/s: Multicentre Study – 3 centres in the Czech Republic, 1 centre in the Slovak Republic	
Study period: Est. date of first enrolment: February 2009 Est. date of last completed: May 2009	**Phase of development:** N/A
Objectives: <u>*Primary Objective*</u> *To investigate the efficacy of Captafer (haematologic parameters, s-Fe) in patients with Inflammatory bowel diseases suffering with iron deficiency anaemia* <u>*Secondary Objectives*</u> To assess the Quality of life of IBD patients with secondary anaemia after the treatment compared to baseline The global assessment of the medication	

Name of Company:
Nordic, s.r.o., K Rybniku 475, 252 42 Jesenice u Prahy, Czech Republic

Name of Finished Product:
CAPTAFER ™

Name of Active Ingredient:
Fish cartilage extract

Methodology:

An open-label multicentre study

Visit No.I (day 1):.
After the signature of the Informed Consent the basic demography, medical history will be conducted. Inclusion and Exclusion Criteria will be evaluated.. In case the patient meets criteria for the enrolment into the study, physical examination will be performed, blood samples will be taken for the laboratory examination, The medication for 1 month will be dispensed. The questionnaire on Quality of life will be filled in (see page 6)

Visit No.II (day 30 ±3):
Physical examination will be performed, compliance assessment, adverse events assessment. blood samples will be taken for the laboratory examination. The medication for 1 month will be dispensed. The patient will be asked to fill in the questionnaire on Quality of life (see page 6)

Visit No.III (day 60 ±3):
Physical examination will be performed, compliance assessment, adverse events assessment. blood samples will be taken for the laboratory examination.. The patient will be asked to fill in the questionnaire on Quality of life and Global assessment of the medication (see page 6)

Study restrictions: See sections inclusion and exclusion criteria and Concomitant Medication

Number of subjects (planned and to be analysed):
80 enrolled subjects – 20 in each of three clinical centres. The estimated drop-out rate is 20% maximum (at least 64 evaluable subjects).

Name of Company:
Nordic, s.r.o., K Rybniku 475, 252 42 Jesenice u Prahy, Czech Republic

Name of Finished Product:
CAPTAFER ™

Name of Active Ingredient:
Fish cartilage extract

Main criteria for inclusion/exclusion

Inclusion Criteria

- Written informed consent obtained
- Chronic Crohn s disease with Harvey-Bradshaw score ≤ 6 or chronic ulcerative colitis with Mayo score ≤ 4
- Sideropenic anaemia associated with IBD with hemoglobin values 90 -120 g/l
- Subjects between 18 – 60 years, both sexes
- Ability to read, comprehend, and record information required by protocol.

Exclusion Criteria

- Crohn s disease with Harvey-Bradshaw score > 6 or ulcerative colitis with Mayo score > 4
- Any other disease or condition which may interfere with study assessments as judged by the investigator
- Subject has a history or presence of significant organ disease
- Any kind of bleeding including occulte bleeding
- Vegetarians and vegans
- Subjects with history of any kind of food allergy
- Subjects likely not to comply with the study procedures or with difficulties to understand the study procedures as judged by the investigator
- Subjects taking part in any other clinical trial or having participated in a clinical trial within the previous 3 months
- Pregnant or brest-feeding women

Test product, dose and mode of administration, batch number:

CAPTAFER ™

Dosage form:	tablets
Description of the dosage form:	Off- white oblong biconvex tablet
Strength:	684 mg
Manufacturer:	Medestea, Italy
Daily dose:	one tablet twice daily with meals

Batch number: xxx

Duration of treatment:
2 months

Name of Company:
Nordic, s.r.o., K Rybniku 475, 252 42 Jesenice u Prahy, Czech Republic

Name of Finished Product:
CAPTAFER ™

Name of Active Ingredient:
Fish cartilage extract

Reference therapy, dose and mode of administration, batch number:
N/A

Criteria for evaluation:

Efficacy:

Primary Efficacy variables:

Serum iron – s-Fe will be analysed at baseline and during Visits II (month 1). and III (month 2), the values will be compared by pairing the baseline group with the Month 1 group and Month 2 group respectively.

Secondary Efficacy variables:

Haemoglobin: will be analysed at baseline , during Visits II (month 1). and III (month 2), the values will be compared by pairing the baseline group with the Month 1 group and Month 2 group respectively

Serum Ferritin will be analysed at baseline , during Visits II (month 1). and III (month 2), the values will be compared by pairing the baseline group with the Month 1 group and Month 2 group respectively

Quality of Life

The questionnaire on QoL will be recorded at each visit – the standardized WHOQOL-BREF Questionnaire, the score will be compared by pairing the baseline group with the Month 1 group and Month 2 group respectively.

Global Assessment of Medication: At Visit III the question "How would you rate the study medication"? " 0=poor, 1=fair, 2=good, 3=very good, 4= excellent

Safety:

Analyses of incidence and type of adverse events during the trial period will be done.

Pharmacokinetics:

Not applicable to this trial

Pharmacodynamics:

Not applicable to this trial

Name of Company: Nordic, s.r.o., K Rybniku 475, 252 42 Jesenice u Prahy, Czech Republic
Name of Finished Product: CAPTAFER ™
Name of Active Ingredient: Fish cartilage extract
Statistical evaluation: Xxxxxxxxxxxxxxxxxxxxxx Xxxxxxxxxxxxxxxxxxxxxxx Xxxxxxxxxxxxxxxxxxxxxxxxxxx
Date of the protocol: 12 th January 2009

Patient evaluation schedule:

Evaluation	**Visit I** **Day 1**	**Visit II** **Day30 (+- 3 days)**	**Visit III** **Day 60 (+- 3 days)**
Informed Consent	X		
Evaluation of Incl. and Excl.criteria	X		
Medical History	X		
Demographics	X		
QoL questionnaire- WHOQOL-BREF	X	X	X
Global assessment of the medication			X
Serum iron, serum ferritin, TIBC	X	X	X
FW	X	X	X
Haemoglobin, Hematocrit, No. of Erythrocytes, MCV, MCHC, RDW	X	X	X
CRP	X	X	X
Adverse Events Assessment	X	X	X
Delivery of Medication to Patient	X	X	
Compliance Assesment		X	X