Study Results Synopsis

Open-Label, Multi-Centre, Pilot, Phase II Clinical Study on the Efficacy and Safety of Different Doses of Udenafil in Cirrhotic Patients with Portal Hypertension

Original title: *Double-Blind, Randomised, Parallel-Group, Placebo-Controlled, Multi-Centre Phase II Clinical Study on the Efficacy and Safety of Different Doses of Udenafil in Cirrhotic Patients with Portal Hypertension Preceded by an Open-Label Pilot Phase*

Project No.:	UDT-1/PHT
EudraCT No.:	2006-006393-14
Short title:	Udenafil tablets in portal hypertension
Investigational drug:	Udenafil tablets (12.5/25/50/75 mg tablets)
Reference drug:	Placebo tablets (originally planned)
Indication:	Portal hypertension
Phase of study:	II
First patient enrolled:	20 May 2008
Last patient completed:	14 Aug 2012
Date of final clinical study report:	06 Mar 2014

Sponsor:
Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg
Germany

Medical Expert / LKP acc. to §40 AMG:
Prof. Dr. med. Tilman Sauerbruch
Universitätsklinikum Bonn
Medizinische Klinik und Poliklinik I
Sigmund-Freud-Straße 25
53127 Bonn Germany

GCP statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

SYNOPSIS

Name of Sponsor/Company	*Individual Study Table*	*(For National Authority Use only)*
Dr. Falk Pharma GmbH	*Referring to Part of the Dossier*	
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

Title of Study:
Open-Label, Multi-Centre, Pilot, Phase II Clinical Study on the Efficacy and Safety of Different Doses of Udenafil in Cirrhotic Patients with Portal Hypertension

Study Centres:
Six centres enrolled patients in the open-label pilot phase: 4 centres in Germany, 1 centre in Lithuania, and 1 centre in Austria.

Study Period:	**Phase of Development:**
First patient enrolled: 20 May 2008 Last patient completed: 14 Aug 2012	II

Objectives:
Primary objective:

- To assess the optimal dose of udenafil tablets for treatment of portal hypertension in patients with liver cirrhosis.

Secondary objectives:

- To assess the safety and tolerability of a dose range of udenafil 12.5 to 100 mg/day administered for portal hypertension in patients with liver cirrhosis.

Methodology:
The open-label phase was conducted with a fixed sample size in each dose step.
After completion of the first 2 dose steps of the open-label pilot phase (udenafil 12.5 and 25 mg/day) 2 further dose steps (udenafil 50 and 75 mg/day) were introduced to the open-label pilot phase with Amendment No. 4. Procedures for passing on to the next dose step and for the recruitment of patients on each dose step were identical on the new dose steps compared to the old dose steps.
After completion of the 4 dose steps of the open-label pilot phase (udenafil 12.5, 25, 50 and 75 mg/day) 1 further dose step (udenafil 100 mg/day) was introduced to the open-label pilot phase with Amendment No. 5. Procedures for passing on to the new dose step were identical compared to the old dose steps. In contrast to the regulation for recruitment of patients to dose steps 12.5, 25, 50 and 75 mg/day, multiple patients could be treated at the same time on the 100 mg/day dose step.
The study was terminated by the Sponsor after the last patient completed the 100 mg dose step of the open-label pilot phase. Thus, no double-blind treatment phase was performed.

Name of Sponsor/Company	*Individual Study Table*	*(For National Authority Use only)*
Dr. Falk Pharma GmbH	*Referring to Part of the Dossier*	
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

Number of Patients (Total and for Each Treatment):

Planned/Adapted during Interim Analyses:

Five patients each were planned to be included in the 12.5, 25, 50 and 75 mg/day dose steps of the open-label pilot phase. Ten patients were planned to be included in the 100 mg/day dose step of the open-label pilot phase.

Analysed in the Open-label Pilot Phase:

Number of patients	**Not treated**	**Udenafil 12.5 mg**	**Udenafil 25 mg**	**Udenafil 50 mg**	**Udenafil 75 mg**	**Udenafil 100 mg**	**Total**
Enrolled	1	5	5	6	8	11	36
Treated	---	5	5	6	8	11	35
Safety	---	5	5	6	8	11	35
FAS	---	5	5	6	6	11	33
PP	---	5	5	5	5	10	30

In total, 36 patients were enrolled in the study. Thirty-five patients received at least 1 dose of study medication and were included in the safety analysis set. Thirty-three patients received at least 1 dose of study medication at Visit 1 (Day 0) and were included in the full analysis set (FAS). Thirty patients of the FAS met the criteria for inclusion in the per-protocol (PP) analysis set (see Statistical Methods in this Synopsis) and were included in this data set.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion Criteria:

- Signed informed consent.
- Man or woman between 18 and 70 years of age.
- Compensated liver cirrhosis as proven by clinical findings, laboratory tests, and ultrasound.

  Liver cirrhosis as proven by histology or FibroScan (facultative) or by unequivocal clinical, radiological and laboratory signs.
- Clinically significant portal hypertension defined as hepatic venous pressure gradient (HVPG) ≥12 mmHg.

Main Exclusion Criteria:

- Child-Pugh C.
- Existing transjugular intrahepatic portosystemic shunt or surgical shunt.
- Splenic or portal vein thrombosis by Doppler ultrasonography, magnetic resonance imaging.
- Gastric/duodenal varices with bleeding stigmata or gastric/duodenal varices with history of bleeding.
- Large oesophageal varices (≥5 mm in diameter).
- Alcoholic hepatitis.
- Hepatic encephalopathy ≥ stage 2.
- Ascites present at Baseline Visit.
- Total bilirubin >3 mg/dl.
- Bleeding disorder.

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table* *Referring to Part of the Dossier* *Volume:* *Page:*	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient: **Udenafil**		

• Low risk of bleeding characterised by no or small (<5 mm in diameter) oesophageal varices proven by endoscopy.	• Active peptic ulceration. • Anatomical deformation of the penis or penile implants. • Predisposing priapism, sickle cell anaemia, thrombocythaemia, polycythaemia, prone to venous thrombosis, hyperviscosity syndrome. • Known hereditary degenerative retinal disorders. • Previous episode of non-arteritic anterior ischaemic optic neuropathy. • Drugs that could have an effect on splanchnic haemodynamics/portal pressure.

Duration of Treatment:
Open-label pilot phase: 1 week.

Investigational Drug, Dose and Mode of Administration, Batch Number:
Udenafil 12.5 mg tablets
Udenafil 25 mg tablets
Udenafil 50 mg tablets
Udenafil 75 mg tablets (acc. to Amendment No. 4)
Udenafil 2 x 50 mg tablets (acc. to Amendment No. 5)
Open-label pilot phase
Patients in the 1st dose step were to take 1 udenafil 12.5 mg tablet per day.
Patients in the 2nd dose step were to take 1 udenafil 25 mg tablet per day.
Patients in the 3rd dose step were to take 1 udenafil 50 mg tablet per day. (acc. to Amendment No. 4)
Patients in the 4th dose step were to take 1 udenafil 75 mg tablet per day. (acc. to Amendment No. 4)
Patients in the 5th dose step were to take 2 udenafil 50 mg tablets per day. (acc. to Amendment No. 5)
Udenafil tablets were to be taken orally with breakfast in the morning.
Batch numbers (fictitious batch number: UD011206):

Udenafil 12.5 mg tablets:	2006M115A	Expiry date: 12/2008
Udenafil 25 mg tablets:	2006L101A	Expiry date: 12/2008, 05/2009 (2 relabellings)
Udenafil 50 mg tablets:	2008J136A	Expiry date: 10/2010, 7/2012 (2 relabellings)
Udenafil 75 mg tablets:	2008K147A	Expiry date: 10/2010, 10/2011(1 relabelling)

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table* *Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

Criteria for Evaluation:

Primary Efficacy Variable:

- Rate of patients showing response defined as final HVPG reduction by ≥20% compared to Baseline or final HVPG reduction to ≤12 mmHg.

Secondary Efficacy Variables:

- Change of HVPG one hour after intake of udenafil on day 0 and day 6 (acute setting)
- Rates of patients with final HVPG reduction of ≥10% and ≥20%, respectively, compared to day 0
- Changes in liver function

Safety:

- Adverse events.
- Vital signs (blood pressure, heart rate) and body weight.
- Influence on systemic blood pressure.
- Mean arterial pressure.
- Influence on heart rate.
- Symptomatic hypotension.
- Clinical laboratory tests: haematology, blood chemistry, urinalysis.
- Renal function.
- Assessment of tolerability by investigator and patient.

Statistical Methods:

Evaluations of efficacy and safety variables were analyzed in an exploratory sense. Descriptive statistical methods were used to analyze the variables. For testing of the absolute and relative change of HVPG and mean arterial pressure, the signed rank test for comparing two time points was used.

For statistical analysis 3 data sets were defined: The safety data set (all patients who received at least 1 dose of study medication), the full analysis set (FAS) (all patients who received at least 1 dose of study medication at Visit 1 (Day 0)), and the per-protocol (PP) data set (all patients of the FAS who met the following criteria: no premature withdrawal, complete HVPG and technically correct measurements, intake of all study medication between Day 0 and Day 6, no intake of forbidden prior/concomitant medication).

In case of missing HVPG values of the 3 measurements per visit, these values were replaced by the average of the available values. No other missing values were replaced.

Name of Sponsor/Company	*Individual Study Table*	*(For National Authority Use only)*
Dr. Falk Pharma GmbH	*Referring to Part of the Dossier*	
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

Summary:

Patient Disposition:

In total, 36 patients were enrolled in the study. Thirty-five patients received at least 1 dose of study medication and were included in the safety analysis set. Thirty-two patients completed the study according to Protocol. Three patients were prematurely withdrawn, 1 patient of the udenafil 50 mg group due to an intolerable AE (upper intestinal bleeding), 2 patients of the udenafil 75 mg group because HVPG was not elevated (<12 mmHg).

Baseline demographic data of patients in the per-protocol set.

		12.5 mg n=5	**25 mg n=5**	**50 mg n=5**	**75 mg n=5**	**100 mg n=10**
Sex						
Male	n	4	4	3	3	5
Female	n	1	1	2	2	5
Age [years]	Mean (SD)	44.6 (8.8)	58.0 (7.3)	56.6 (7.1)	47.0 (6.7)	48.7 (12.2)
Weight [kg]	Mean (SD)	89.2 (20.6)	77.1 (15.4)	78.3 (15.2)	83.1 (19.7)	80.6 (18.3)
Cause of cirrhosis						
alcoholic	n	3	4	2	2	1
nonalcoholic	n	2	1	3	3	9
Disease duration [years]	Median (Range)	4 (3-18)	5 (1-7)	5 (0-10)	4 (1-9)	5 (0-9)
Variceal history						
former variceal bleeding epsiodes	n	0	2	1	0	1
Successful former endoscopic treatment	n	0	3	1	0	1
Child-Pugh score	Mean (SD)	5.0 (0.0)	6.0 (1.7)	6.0 (1.2)	5.4 (0.9)	5.8 (1.6)

SD: standard deviation

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table* *Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

Efficacy Results:

Data of HVPG measurements are indicated in following table. Since the data suggested that both, 75 mg udenafil and 100 mg udenafil effectively reduced HVPG in the acute setting, a further evaluation was done in a combined dosage group. Reduction of HVPG by ≥20% or to ≤12 mmHg from day 0 pre-dose to day 6 post-dose was reached in 3/5, 2/5, 2/5, 1/5, 4/10, and 5/15 patients in the groups with 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, and in the combined group.

HVPG at the different time points:

		All patients n=30	12.5 mg n=5	25 mg n=5	50 mg n=5	75 mg n=5	100 mg n=10	75 & 100 mg n=15
HVPG Day 0	pre-dose [mm Hg]	18.0 ± 4.8	14.3 ± 4.0	20.9 ± 4.4	22.9 ± 4.5	19.1 ± 4.8	15.5 ± 2.7	16.7 ± 3.8
	1 h post-dose [mm Hg]	16.0 ± 6.1	13.9 ± 4.7	20.0 ± 5.4	21.2 ± 6.0	15.1 ± 7.4	12.9 ± 4.4	13.6 ± 5.4
	absolute change [mm Hg]	-2.0 ± 3.3	-0.4 ± 1.7	-0.9 ± 3.7	-1.7 ± 4.2	-4.0 ± 3.0	**-2.6 ± 3.3**[1]	**-3.1 ± 3.2**[2]
	relative change %	-12.5 ± 20.6	-3.5 ± 11.9	-4.5 ± 17.5	-7.5 ± 19.8	-25.1 ± 22.2	**-17.3 ± 23.8**[3]	**-19.9 ± 22.8**[4]
HVPG Day 6	pre-dose [mm Hg]	17.6 ± 6.7	13.6 ± 6.6	22.6 ± 8.9	20.9 ± 4.1	18.3 ± 4.2	15.2 ± 6.2	16.2 ± 5.6
	1 h post-dose [mm Hg]	16.1 ± 6.6	12.3 ± 4.4	22.3 ± 9.4	19.5 ± 4.3	16.3 ± 4.1	13.0 ± 5.7	14.1 ± 5.3
	absolute change [mm Hg]	-1.6 ± 2.7	-1.3 ± 3.4	-0.3 ± 3.0	-1.3 ± 2.8	-2.1 ± 1.8	**-2.1 ± 2.9**[5]	**-2.1 ± 2.5**[6]
	relative change %	-7.7 ± 20.0	-0.3 ± 28.5	-2.5 ± 14.5	-6.0 ± 15.1	-11.4 ± 10.6	-12.9 ± 24.3	**-12.4 ± 20.3**[7]
abs. change of HVPG (day 6 post-dose vs. day 0 pre-dose) [mm Hg]		-2.0 ± 4.1	-2.0 ± 2.0	1.4 ± 5.3	-3.4 ± 4.1	-2.8 ± 2.5	-2.5 ± 4.7	**-2.6 ± 4.0**[8]
relative change of HVPG (day 6 post-dose vs. day 0 pre-dose) %		-12.0 ± 23.1	-14.4 ± 14.9	3.1 ± 24.9	-14.0 ± 16.5	-13.5 ± 16.2	-16.8 ± 30.9	**-15.7 ± 26.3**[9]
Reduction of HVPG by ≥20% or to ≤12 mmHg from day 0 pre-dose to day 6 post-dose		12/30	3/5	2/5	2/5	1/5	4/10	5/15

Absolute and relative changes of HVPG (mean ± SD). [1]p=0.012; [2]p=0.0004; [3]p=0.014; [4]p=0.0006; [5]p=0.045; [6]p=0.008; [7]p=0.042; [8]p=0.023; [9]p=0.040

Systemic haemodynamic effects

Data on systolic, diastolic, and mean arterial blood pressure (MAP), and heart rate are shown in table below. In the 100 mg group, MAP, the clinically most relevant parameter, decreased from pre-dose to post-dose on day 0 by 3.8 ± 5.1% (3.9 mmHg [p = 0.049]) and by 6.0 ± 7.4% (6.2 mmHg [p = 0.037]) on day 6. These changes of MAP were well tolerated by all patients. Heart rate remained unchanged.

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product:	*Volume:*	
Name of Active Ingredient: **Udenafil**	*Page:*	

Systemic hemodynamic parameters:

Parameter (mean ± SD)		12.5 mg n=5	25 mg n=5	50 mg n=5	75 mg n=5	100 mg n=10	75 & 100 mg n=15
Systolic blood pressure [mmHg]	Day 0 pre-dose	125.4 ± 9.7	136.6 ± 6.5	122.0 ± 10.4	126.6 ± 18.8	135.2 ± 13.6	132.3 ± 15.4
	Day 0 post-dose: percent change to day 0 pre-dose	4.8 ± 6.8	-4.7 ± 10.2	-1.9 ± 2.6	-5.5 ± 5.4	-4.2 ± 6.5	-4.6 ± 6.0
	Day 6 post-dose: percent change to day 0 pre-dose	7.0 ± 9.9	-5.4 ± 11.2	0.7 ± 4.2	-7.0 ± 9.4	-7.0 ± 9.4	-7.0 ± 9.1
Diastolic blood pressure [mmHg]	Day 0 pre-dose	75.8 ± 11.5	80.2 ± 9.4	78.8 ± 6.9	75.6 ± 9.2	80.7 ± 5.9	79.0 ± 7.3
	Day 0 post-dose: percent change to day 0 pre-dose	6.1 ± 9.0	-5.9 ± 4.0	-1.0 ± 7.5	-2.9 ± 7.9	-3.4 ± 5.2	-3.2 ± 5.9
	Day 6 post-dose: percent change to day 0 pre-dose	6.3 ± 8.1	-11.2 ± 10.6	-0.9 ± 7.2	-3.4 ± 12.9	-5.0 ± 7.7	-4.5 ± 9.3
MAP [mmHg]	Day 0 pre-dose (mmHg)	92.3 ± 10.6	99.0 ± 8.4	93.2 ± 7.6	92.6 ± 12.0	98.9 ± 8.1	96.8 ± 9.6
	Day 0 post-dose: percent change to day 0 pre-dose	5.5 ± 7.5	-5.3 ± 6.0	-1.4 ± 5.2	-4.2 ± 6.3	**-3.8 ± 5.1[1]**	**-3.9 ± 5.3[2]**
	Day 6 pre-dose (mmHg)	94.0 ± 13.7	91.8 ± 5.9	93.8 ± 7.2	89.9 ± 13.4	92.8 ± 7.7	91.8 ± 9.6
	Day 6 post-dose: percent change to day 6 pre-dose	5.1 ± 8.5	-1.9 ± 6.3	-1.0 ± 2.8	-2.1 ± 9.3	0.1 ± 6.5	-0.7 ± 7.3
	Day 6 pre-dose: percent change to day 0 pre-dose	1.6 ± 6.0	-6.6 ± 10.9	0.7 ± 3.9	-3.0 ± 4.6	**-5.9 ± 6.3[3]**	**-5.0 ± 5.8[4]**
	Day 6 post-dose: percent change to day 0 pre-dose	6.6 ± 8.3	-8.6 ± 9.9	-0.2 ± 5.5	-5.0 ± 10.9	**-6.0 ± 7.4[5]**	**-5.7 ± 8.3[6]**
Heart rate [bpm]	Day 0 pre-dose	80.6 ± 8.4	79.2 ± 11.4	80.8 ± 11.0	74.8 ± 7.1	73.3 ± 5.9	73.8 ± 6.1
	Day 0 post-dose: percent change to day 0 pre-dose	0.86 ± 2.2	2.5 ± 13.7	-3.4 ± 16.4	-6.9 ± 4.8	-4.7 ± 7.9	-5.5 ± 6.9
	Day 6 post-dose: percent change to day 0 pre-dose	-15.0 ± 5.8	-4.4 ± 11.9	-4.9 ± 9.9	-5.9 ± 11.8	-3.8 ± 11.7	-4.5 ± 11.3

SD: standard deviation. MAP: mean arterial pressure. bpm: beats per minute.
[1]p=0.049; [2]p=0.010; [3]p=0.014; [4]p=0.005; [5]p=0.037; [6]p=0.022

Safety Results:

Adverse events:

In total, 9 patients (25.7%) experienced at least 1 treatment-emergent AE (TEAE), i.e., 2 (40.0%), 1 (20.0%), 2 (33.3%), 1 (12.5%), and 3 (27.3%) patients in the udenafil 12.5, 25, 50, 75, and 100 mg groups. Most patients experienced gastrointestinal disorders (4 patients (11.4%)). The majority of patients experienced TEAEs of mild or moderate intensity. Severe TEAEs occurred in 1 patient in the udenafil 25 mg group (calculus urethral) and 1 patient in the udenafil 50 mg group (upper gastrointestinal haemorrhage).

Name of Sponsor/Company	*Individual Study Table*	*(For National Authority Use only)*
Dr. Falk Pharma GmbH	*Referring to Part of the Dossier*	
Name of Finished Product:	*Volume:*	
Name of Active Ingredient:	*Page:*	
Udenafil		

All TEAEs were assessed by the investigator as unlikely or not related to the intake of study medication. No TEAE was a suspect adverse drug reaction (assessed as certainly, probably, or possibly related to intake of udenafil).

No patient died during the course of this study. In 3 patients (8.6%) there were serious TEAEs: calculus urethral in 1 patient in the udenafil 25 mg group, upper gastrointestinal haemorrhage in 1 patient in the udenafil 50 mg group, and lower gastrointestinal haemorrhage in 1 patient in the udenafil 100 mg group. The patient with an upper gastrointestinal haemorrhage was discontinued from the study due to the serious TEAE.

Laboratory safety parameters:

The most prominent changes from baseline to Visit 7 were observed for parameters of cholestasis (decrease in total and direct bilirubin, alkaline phosphatase, and GGT). Furthermore, erythrocytes, haemoglobin, haematocrit, LDH, and AST showed a slight decrease of around 5% each from baseline to Visit 7 and plasma glucose showed a slight increase from baseline to Visit 7 associated with a relevant number of patients showing a change to values above the normal range.

Vital signs and Electrocardiogram:

Most prominent was a decrease in systolic blood pressure from pre-dose to 1 hour postdose at Visit 1. Decreases in diastolic blood pressure or mean arterial pressure were less pronounced.

Global assessment of tolerability:

Tolerability of the study medication was assessed as very good or good in the vast majority of patients by both the investigators and patients. None of the investigators or patients rated tolerability of the study medication as poor.

Conclusions:

- Udenafil caused a reduction of HVPG in cirrhotic patients with portal hypertension already at a dosage of 12.5 mg/d but most pronounced at a dosage of 100 mg/d.
- Udenafil at a dosage of 100 mg/d led to a statistically significant reduction of portal pressure both on Day 0 and Day 6 in the acute setting.
- Udenafil in an oral daily dose of up to 100 mg/d was well tolerated in cirrhotic patients (Child A or B) with portal hypertension during a treatment of 7 days.
- No relevant cardiovascular side effects were observed, especially no relevant lowering of mean arterial pressure.
- The role of udenafil as a potential novel treatment for portal hypertension cannot be reliably assessed on the basis of this study, due to the small sample size, the open design, the lack of a control group, and the short treatment duration.
- Further studies are necessary before embarking a long-term study for prevention of bleeding episodes in patients suffering from portal hypertension.

Publication:	*Kreisel W, Deibert P, Kupcinskas L, et al. The phosphodiesterase-5-inhibitor udenafil lowers portal pressure in compensated preascitic liver cirrhosis. A dose-finding phase-II-study. Dig Liver Dis. 2015;47(2):144-50.*