INTEGRATED CLINICAL AND STATISTICAL STUDY REPORT

Comprehensive Report on Final Analysis

Trial to Evaluate the Efficacy of Rowatinex on Elimination of Fragments of Calculi Generated by ESWL
A Placebo Controlled, Multi-centre Study

Version, Date:	1.0 (Final), 16 February 2009
Protocol No. / IMEREM ID:	Rowatinex / 2002 / HU; S59-NEP-051
Study Drug, Dosage:	2 capsules à 100mg, TID
Clinical Phase:	IV
Indication Studied:	Nephrolithiasis after complication-free ESWL
Principal Investigator:	Prof. Dr. Imre Romics Department of Urology Semmelweis University Budapest, Üllői út 78/B H-1082 Hungary
Sponsor:	ROWA Pharmaceuticals Ltd. Newtown Bantry, Co. Cork, Ireland SATCO Ltd. Multi Plaza, Fehérvári út 89-95 H-1119 Budapest, Hungary
CRO:	IMEREM GmbH Scheurlstr. 21 90478 Nürnberg, Germany
Key Dates:	Study Protocol: 25 JUN 2002 *Amendment 1:* 07 JUN 2004 *Amendment 2:* 15 FEB 2005 *Amendment 3:* 17 OCT 2005 First Patient In: 26 JUN 2003 Last Patient Out: 01 DEC 2006

1 SIGNATURE PAGE

Study Title: Trial to Evaluate the Efficacy of Rowatinex on Elimination of Fragments of alculi Generated by ESWL. A Placebo Controlled, Multi-centre Study

Study Code: Rowatinex / 2002 / HU

INVESTIGATOR DECLARATION

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and the results of the study.

Coordinating Investigator: _____ 27. FEB. 2009
Date

Prof. Dr. Imre Romics
Department of Urology
Semmelweis University
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H-1082 Budapest, Hungary

COMPANY DECLARATION

The undersigned confirm that this report to the best of their knowledge accurately describes the conduct and the results of the study.

Project Manager
(Sponsor): _____ 04 MARCH 2009
Date

Arpad Kiss for:
Rowa Pharmaceuticals Ltd.
Newtown
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Biostatistician /
Report Author (CRO): _____ 16 Feb 2009
Date

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2 STUDY SYNOPSIS

Title of Study:	Trial to Evaluate the Efficacy of Rowatinex on Elimination of Fragments of Calculi Generated by ESWL. A Placebo Controlled, Multi-centre Study
Study Code/IMEREM ID:	Rowatinex/2002/HU; S59-NEP-051
Name of Finished Product:	Rowatinex®
Name of Active Ingredient:	Pinene (α+β) 31.0 mg, Camphene 15.0 mg, Borneol 10.0 mg, and other substances
Development Phase:	IV
Sponsor:	Rowa Pharmaceuticals Ltd., Newtown, Bantry, Co. Cork, Ireland Satco Trading Co Ltd., Multi Plaza, Fehérvári út 89-95, Budapest, Hungary
Coordinating Investigator:	Prof. Dr. Imre Romics Dept of Urology, Semmelweis University, Üllői út 78/B, H-1082 Budapest, Hungary
Medical Expert:	Dr. György Siller Urology Surgery, Károlyi Sándor Hospital, Baross út 69-71, H-1047 Budapest, Hungary
Study Centres:	2 urology clinics in Budapest plus 4 other centres in Hungary enrolled and treated study patients
Publication (References):	None
Study Period:	First patient in 26 JUN 2003 Last patient out 01 DEC 2006
Objectives:	The objectives of this study were to evaluate the safety and efficacy of Rowatinex (3x2 capsules/day) and placebo in the treatment of nephrolithiasis patients by measuring the effect on the parameters given below:
Primary:	• Stone-free status 12-weeks after ESWL • Rate of patients requiring surgical intervention due to complications or residual stone
Secondary:	The major secondary study objectives were: • Time to stone-free status • Efficacy of pain control • Rate of clinically insignificant and clinically significant residual stones • Frequency of Adverse Events • Frequencies of ESWL complications including clinical symptoms
Design:	Multi-centre, randomized, double-blind therapeutic, parallel group trial to demonstrate superiority of Rowatinex versus Placebo with respect to efficacy and to compare safety of both treatments.

Study Schedule:	The study consists of a screening phase, a 12-week treatment phase and a 2-week follow-up phase.	
Total Number of Patients (Planned and Analyzed):	Planned for analysis:	222 (Rowatinex: 111, Placebo: 111)
	Safety Analysis:	222 (Rowatinex: 112, Placebo: 110)
	ITT Analysis:	204 (Rowatinex: 106, Placebo: 98)
	PP Analysis:	180 (Rowatinex: 92, Placebo: 88)
Diagnosis and Main Criteria for Inclusion:	Inclusion criteria: complication-free ESWL indicated by complication-free calculus, no urinary deviation (PCN, DJ), kidney stone (longest diameter) smaller than or equal to 20 mm, no endourological intervention before ESWL, X-ray negative, stones are visualised by US targeting, no obstruction, no severe untreated associated disease, age older than 18 years, signed informed consent. Exclusion criteria: complication due to kidney stone: severe colic, anuria or severe infection of the urinary tract, known allergy to terpenes or other components of the trial medication, pregnancy, lactation.	
Medication:	Test product	Comparator
Trade name:	Rowatinex® (liquid)	n.a.
Active agent:	Each 100mg capsule contains: Pinene (α+β) 31.0 mg, Camphene 15.0 mg, Cineol 3.0 mg, Fenchone 4.0 mg, Borneol 10.0 mg, Anethol 4.0 mg	n.a.: placebo
Drug form:	capsules, soft-enteric-coated gelatine	capsules, soft-enteric-coated gelatine
Route of administration:	p.o. (oral)	p.o. (oral)
Dosage:	2 capsules à 100mg TID	2 capsules TID
Batch No:	5084C-14, 5789C-15, 5793C-16,	4622C-5, 5851C-2, 5815C-3
Manufacterer, MAH:	Rowa Pharmaceuticals Ltd. Newtown, Bantry, Co. Cork Ireland	Rowa Pharmaceuticals Ltd. Newtown, Bantry, Co. Cork Ireland
Duration of Treatment:	The study drug was to be administered over a period of 3 months (12 weeks).	
Criteria for Evaluation:		
Efficacy:	Primary efficacy criteria: • Rate of stone-free patients within 3 months after ESWL • Rate of patients requiring surgical intervention due to complications or residual stones Secondary efficacy criteria: • Time to stone-free status within 3 months after ESWL • Efficacy of pain control (VAS), change from Visit 1 to final assessment. • Pain control as assessed by 50% responder and remitter (pain = 0) rate • Rate of clinically insignificant and clinically significant residual stones • Frequency of complications requiring surgery	

	• Frequencies of ESWL complications including clinical symptoms • Rate of stone-free patients within 3 months after ESWL stratified by ultrasound and X-ray of kidney, ureter and bladder • Subgroup analysis: both primary endpoints will be analyzed stratified by (a) size of stone (≤ 8 mm vs. > 8 mm) and (b) position of stone at screening
Safety:	• Frequency and severity of adverse events and serious adverse events • Clinical notable abnormalities in laboratory tests • Vital signs: change from baseline and clinically notable abnormalities in blood pressure, pulse, and weight
Statistical Methods:	**Estimation of Sample Size and Decision Strategy for Interim Analysis:** For final analysis of the complete trial, 222 patients were to be enrolled. This was expected to provide 80% power to detect 20% group difference in the proportion of stone-free status at Week 12, with a 5% probability of Type I error rate while assuming 70% success rate in the Rowatinex group. Final sample size was derived from an adaptive interim analysis after 141 (Safety population) respectively 122 (ITT population) patients. **Efficacy Analysis:** Analysis of primary efficacy was to demonstrate that 12 weeks of treatment with 3×2 Rowatinex capsules after ESWL were superior as compared to 3×2 capsules placebo (a) in a higher "rate of stone-free status of patients until week 12" and (b) a lower rate of patients requiring surgical interventions due to complications or residual stones under active treatment. Rate of patients was analyzed with a chi^2 test and the complication rate by a logistic regression, fitting terms for treatment group and center. Primary efficacy analysis was performed with the ITT on the one-sided 2.5% level. Due to the interim analysis an adaptive test design according to Bauer & Köhne was applied, Type I-error was adjusted to a 1-sided p=0.0038. Exploratory tests included the log-rank test for Kaplan-Meier analyses and 2-sample tests for continuous and categorical data. Besides the ITT population, also the PP population and the completer (12-weeks treatment + 2 weeks follow-up) set were analyzed to investigate robustness of Rowatinex efficacy. **Safety Analysis:** Safety data are presented in a descriptive manner.

Efficacy Results:

Demographic and Clinical Baseline Characteristics:

Slightly more men (56%) than women participated in the study. Median age was 49 years, ranging from 18 to 82 years. Half of the patient had previous ESWL (50.9%). If pretreated, most frequently 3 previous ESWL had been applied.

Analysis of the Primary Efficacy Criteria:

Rate of patients with stone-free status

In the Rowatinex-group, 67.9% of the patients were stone-free at the last assessment, in the placebo group, there were 50.0. Rowatinex was statistically superior to placebo as shown by a 1-sided p-value of p=0.0009, derived from the adaptive procedures within a 2-stage analysis according to Bauer & Köhne, which was below the critical boundary of a 1-sided p=0.0038 Based on a difference of 17.9%, the NNT (number needed to treat) is 5.6, which is clinically relevant. The more favourable efficacy of Rowatinex compared to placebo in the primary endpoint as decribed for the ITT population is even more pronounced in PP population with a difference of 26.12% more responder under Rowatinex than under placebo and a clinically highly significant NNT = 3.8.

Surgical interventions due to complications

The second primary efficacy criterion had not been analyzed because only two patients of the Rowatinex group were affected by a surgical intervention.

Analysis of the Secondary Efficacy Criteria:

Time to stone-free status within 12 weeks after ESWL

From Kaplan-Meier-analyses, the median time for patients to become stone-free in this trial was 56 days in the Rowatinex-group, 85 days in the placebo-group. This difference of approximately one month was statistically significant (1-sided p=0.0016 < p=0.0038), applying the same procedure for an adaptive analysis as decribed for the rate of stone-free patients.

Pain measured by a visual analogue scale

Pain improved remarkably during treatment to a similar extent in both treatment groups which were comparable both in changes between baseline and last assessment as well as in the responder and remitter rates.

Number of residual stones

According to the ultrasound assessments, four of five patients had resudial stones at baseline. At the end of the trial, tendentially less patients in the Rowatinex group (27%) than in the placebo group (40%) had still stones detectable by ultrasound (p=0.09945).

Frequency distributions of different surgical interventions, ESWL complications, and clinical signs

Only two patients of the Rowatinex group needed surgical interventions, both suffered from fever, pyelonephritis and occlusion. Also other complications were rare, and clinical signs like nausea or headache were reported in less than 5% in either treatment group.

Subgroup analysis

Differences between Rowatinex and Placebo were similar in subgroups when the largest initial stone at the time of ESWL was stratified into smaller and larger stones. (largest diameter of $\leq$ 8 mm vs. > 8 mm), however, more patients became stone-free when their kidney stone was below 8 mm. Rowatinex seems to be more effective in stones in the upper and lower left and right calyx compared to the middle calyx and the Pyelum passage.

Safety Results:

Adverse events

Twenty-five AEs occurred in the Rowatinex group and 27 in the placebo group. In the Rowatinex group seven of these AEs were assessed as drug related, in the placebo group two AEs were suspected to be drug related. Four serious AEs (SAEs) occurred during the trial, three of them under Rowatinex treatment but none was considered drug-related..

Most frequently recorded AEs were gastrointestinal disorders followed by disorders of the renal and urinary tract. For both system organ classes a little higher number of AEs was observed in the placebo group than in the Rowatinex group (8.2 % vs. 5.4 % for gastrointestinal disorder and 4.5% vs. 2.7 % for renal and urinary disorders, respectively).

Laboratory parameters

Only very few patients were developing significant abnormal laboratory values (assessed by the investigator as clinically significant deviation from normal range) during the study. The majority of patients did not develop abnormal values at baseline and/or at the end of treatment (last measure).

Vital signs

Both for vital signs blood pressure and heart rate as well as for body temperature no statistical differences for the raw values could be found between the treatment groups at baseline and end of treatment. No frequent significant changes were reported from baseline to end of treatment. No clinically notable abnormalities were observed during the study.

Conclusion:	Rowatinex is an efficacious treatment in eliminating calculi fragments generated by ESWL as compared to placebo after 12-weeks of theapy. Treatment with Rowatinex is well tolerated and safe.
Date of the Report:	16 February 2009 (Final V1.0)

3 TABLE OF CONTENTS

3.1 Contents of Study Report

16 APPENDICES

16.1 Study Information

- 16.1.1 Protocol and Protocol Amendments
- 16.1.2 Sample Case Report Form (Unique Pages only)
- 16.1.3 List of IECs or IRBs
- 16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
- 16.1.5 Signatures of Principal or Co-ordinating Investigator(s) or Sponsor's responsible medical officer depending on the regulatory authority's requirement
- 16.1.6 Randomization scheme and codes (patient identification and treatment assigned)
- 16.1.7 Audit certificates
- 16.1.8 Documentation of statistical methods
- 16.1.9 Documentation of laboratory quality assurance procedures
- 16.1.10 Publications based on the study
- 16.1.11 Important publications referenced in the report

16.2 Tables

16.3 Figures (as available)

16.4 Listings

16.5 Case Report Form

3.2 List of Tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

α	Type 1 error
β	Type 2 error
AE	Adverse event
AMG	Arzneimittelgesetz (German Drug Law)
ANCOVA	Analysis of Covariance
AP	Apatit
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
CCSI	Company Core Safety Information
CRF	Case Report Form
CS	Completer Set
CT	Computerised tomography
ESWL	Extracorporeal Shockwave Lithotripsy
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-to-treat
LOCF	Last observation carried forward
PCNL	Percutaneous Nephrolithotomy
PL	Placebo
PP	Per-Protocol
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical Analysis Plan
SDL	Subject data listing
SEC	Self-evident correction
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Serious unexpected suspected adverse reaction
SW	Shockwave
VAS	Visual Analogue Scale
WD	Weddellit
WHO	World Health Organization
WW	Whewellit

5 ETHICS AND GOOD CLINICAL PRACTICE

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The trial protocol, subject information leaflet, and subject informed consent were reviewed and approved by the ethics committees responsible for each investigator and study site (a list of Ethic Committees involved is provided in Appendix 16.1.3):

5.2 Ethical Conduct of the Study

The clinical study was planned, conducted and analyzed in accordance with the following documents:

- ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) of the International Conference on Harmonization (ICH guideline E6, 01 MAY 1996)
- Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community
- Declaration of Helsinki (1964) and its updates of Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), and Edinburgh (2000).

In addition, the study was conducted in accordance with Hungarian laws and OGYI regulations.

Prior to the initiation of the trial the Sponsor took out an insurance policy (maximum compensation: HUF 200.000,- per subject) with HUF 5 million by Allianz Hungária (policy number: FXF 350.226 136.210 for all the subjects participating in the study. The subjects were informed of the existence of the contract and the obligations pursuant to it.

5.3 Patient Information and Consent

For each trial patient, written informed consent was obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his associates has explained orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient and (if applicable) an appointed guardian were aware of the potential risks, inconveniences, or adverse effects that may occur. They were informed that the patient may withdraw from the study at any time. They received all information that was required by local regulations. The principal investigator at each study site has provided the representative of the sponsor with a copy of the IEC- approved informed consent form prior to the start of the study.

6 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator	Prof. Dr. Imre Romics Department of Urology Semmelweis University Üllői út 78/B H-1082 Budapest, Hungary
Sponsor	ROWA Pharmaceuticals Ltd. Newtown Bantry, Co. Cork, Ireland SATCO Ltd. Multi Plaza, Fehérvári út 89-95 H-1119 Budapest, Hungary
Trial Conduct Team Leader	Dr. Ròbert Kiss Györgyi Kovàcs HungaroTrial CRO Fehérvári út 89-95 H-1119 Budapest, Hungary
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Statistical Programmer	Helmut Kellerer, MSc
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Biostatistician, Report Author	Ralf Kohnen, PhD, Professor

Auditor(s)	Dr. Gábor Bognár Consultant Auditor Királyok útja 297/E H-1039 Budapest, Hungary Phone: ++36 (0)1 / 2436246 Mobile: ++36 20 520 9700
Investigators	For individual investigators / centres confer Appendix 16.1.4
Involved laboratories	For the laboratories confer Appendix 16.1.9

7 INTRODUCTION

Urolithiasis is a common condition which affects approximately 5-12% of the population worldwide (Coe et al., 2005; Healy & Ogan, 2005; Park, 2007, Pietrow & Karellas, 2006). ESWL is the first choice of treatment in the therapy of kidney stones and success rates of greater than 90% have been reported (Dawson & Whitfield, 1994; Kosar et al., 1999; Madaan & Joyce, 2007). Success of treatment is determined by the size of calculus, location, chemical composition, anatomy and functioning of the kidney, type of lythotriptor, the quantity of energy applied, and the experience of the physician. The current understanding is that stone-free should mean exactly that and should not include those patients with asymptomatic (clinically insignificant residual stones) fragments <4mm (Galvin & Pearle, 2006; Tan & Wong, 2005).

Many studies have investigated the role of medical therapies, mainly calcium-channel blockers, α-blockers, and corticosteroids, hormones, and prostaglandin synthetase inhibitors for conservative expulsitory therapy of ureteral stones (Caramia et al., 2004; Healy & Ogan, 2005; Pietrow & Karellas, 2006; Straub & Hautmann, 2004). However, treatment of urinary stones with phytotherapy might be an alternative treatment with effective, safe and culturally acceptable properties (Gurocak & Kupeli, 2006).

The therapeutic use of essential oils and/or terpenes in urolithiasis patients has a long-standing use in phytotherapy because they affect kidney function (e.g., filtration, diuresis and blood circulation) and smooth muscle function. In particular, the use of the special terpene combination Rowatinex® (an essential oil preparation composed of different terpenes; Rowa Pharmaceuticals Ltd., Ireland) in the supportive treatment of urolithiasis (renal and/or ureteral calculi), specifically in conditions with spasm and/or inflammation associated with urolithiasis and for assistance in the expulsion of stones of the renal system has a 50-year history in more than 60 countries all around the world.

The first clinical and pre-clinical investigations of Rowatinex® date back to as early as 1954 and 1956 (Urbainski, 1954; Geinitz, 1956). Since then, expulsion of stones and preventive effects on stone formation were observed as results of Rowatinex® treatment in animal models of nephrocalcinosis (Basagic, 1962; Stern & Vukčević, 1960) and it was shown also in the clinical studies and in post-marketing reports. The *in vitro* and animal studies performed and published so far show that Rowatinex® exhibits anti-lithogen, anti-bacterial, anti-inflammatory, spasmolytic, and analgesic activities which are primarily related to the terpene ingredients and does influence acute and chronic conditions associated with the respective illnesses of the urinary tract.

The aim of this multi-centre, randomized, double-blind, parallel group trial was to demonstrate superiority of Rowatinex® as compared to placebo with respect to the rate of stone-free patients during 12 weeks of treatment after ESWL.

8 STUDY OBJECTIVES

The objectives of this study were to evaluate the safety and efficacy of Rowatinex (3 x 2 capsules /day) and placebo in the treatment of nephrolithiasis patients.

8.1 Primary Objective

The aim of the study was to demonstrate superiority of Rowatinex in comparison to placebo with respect to efficacy in patients with nephrolithiasis, who received an ESWL therapy. The primary objective criteria for the proof of the efficacy were defined as "rate of patients with stone-free status within 12 weeks after ESWL" for patients with residual stones after ESWL and "residual stones or complications that required surgical intervention" after ESWL and randomization.

The **primary analysis** was performed comparing treatments with respect to these objectives.

Methods: Rate of patients with stone-free status within 12 weeks after ESWL was compared between the two treatments using Fisher's exact test.

A logistic regression, fitting terms for treatment group and center, was applied for proportion of patients with no surgical interventions within 12 weeks after start of treatment. The results were presented as the odds ratio of this rate, the corresponding 95% confidence interval, and the p-value.

8.2 Secondary Objectives

The **secondary efficacy variables** were

- Efficacy of pain-control (VAS), change from Visit 1 to final assessment.
- Pain-control as assessed by 50% responder and remitter (pain = 0) rate.
- Rate of clinically insignificant and clinically significant residual stones.
- Frequency of complications requiring surgery.
- Frequencies of ESWL complications including clinical symptoms.
- Time to stone-free status within 12 weeks after ESWL.
- Rate of stone-free patients within 12 weeks after ESWL stratified by ultra sound and X-ray of kidney, ureter, and bladder.

Secondary variables were analyzed in a descriptive manner both for the ITT and the PP populations.

For pain assessment with the visual analogue scale (VAS), an ANCOVA (analysis of covariance) was performed for the changes from Baseline to end of the final assessment with treatment group as the main factor, baseline as covariate, and center as a classification.

Additionally, a responder and remitter rate assessment was performed for the VAS pain score. A responder was defined as a subject with a decrease of 50% in VAS pain score at the final assessment (week 12 assessment or assessment at the time of premature discontinuation as last available assessment) compared to baseline. A remitter was defined by a VAS pain score = 0 at the final assessment. To compare the two treatment groups, Fisher's exact tests were performed per visit and at endpoint, and p values were provided for descriptive purposes only.

The number of clinically insignificant as well as clinically significant residual stones was compared with a 2-sample Wilcoxon U-test or t-test, or by a Chi-Square contingency test, depending on the distribution of these events. A clinically insignificant residual stone was defined by a stone size smaller than 4 mm without symptoms. A clinically significant residual stone was defined by a stone size smaller than 4 mm with symptoms. Descriptive frequency distributions were provided for the outcome categories of the assessment of residual stones (findings with ultrasound, native kidney image, position, and size of stone).

Time to stone-free status was compared between the two treatment groups using Kaplan-Meier life-table analysis with the log-rank statistic.

Frequency of surgical interventions in general and by category was compared as described for residual stones. In addition, ESWL complications (haematuria, fever, pyelonephritis, occlusion, haematoma) and clinical symptoms (headache, vertigo, nausea, vomiting, eruption) specified in the CRF were compared by binomial tests/Fisher's exact-test including 95% confidence intervals for differences in rates.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Study design:	Multicentre, randomized, double-blind, placebo-controlled with two treatment arms
Type of control:	Placebo concurrent control, parallel-group
Method of treatment assignment:	Randomization, 1:1 ratio
Level of blinding:	Double-blind; patients, investigators, and evaluators blinded

Study population

The study population included male and female patients who were older than 18 years and underwent a complication-free ESWL as indicated by complication-free calculus.

160 patients were planned initially to be assigned on a 1:1 basis to Rowatinex or Placebo. The sample size was increased after a sample size re-calculation to a total of 222 patients (see Amendment 3).

Study centres

About 6 centres in Hungary were to be appointed. These centres had a proven track record of GCP compliance or good compliance.

Duration of observation

The therapy (double-blind treatment phase) started when all data of the baseline-examination were available (Visit 1 - Day 0). The double-blind treatment period was performed until 12 weeks. In case of stone-free status of a patient the study was terminated earlier.

A two week follow-up phase without medication was planned after the medication period. Starting from the date of randomization the patients were observed in the study for a maximum of 14 weeks.

9.2 Discussion of Design, incl. the Choice of Control Groups

This multicentre, randomized, double-blind, placebo-controlled study with two treatment arms was designed following ICH Topic E 9 (CPMP/ICH/363/96) and ICH Topic E 10 (CPMP/ICH/364/96).

The placebo concurrent control design controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug.

The trial was designed for three months active treatment. To date there are no experimental paradigms for the drug treatment of nephrolithiasis following ESWL in which a beneficial effect, whether reversal of signs/symptoms or retardation of disease, has been consistently discerned in periods less than three months.

Rowatinex promotes the disintegration of renal and urinary tract stones and has been shown to prevent stone formation. The biological basis of the present investigation, therefore, was predicated upon the assumption that there is an inherent beneficial effect expressed across indices of dysfunction following the use of Rowatinex.

9.3 Selection of Study Population

9.3.1 Inclusion criteria

To be eligible for the study, patients had to meet all of the following inclusion criteria:

- complication-free ESWL indicated by complication-free calculus,
- no urinary deviation,
- diameter of calculus less than or equal to 20 mm,
- no previous endourological intervention (e.g. nephrostoma, endosplint) before ESWL,
- no urinary tract obstruction,
- no severe untreated associated other disease,
- age older than 18 years,
- signed informed consent.

9.3.2 Exclusion criteria

Subjects were excluded from enrollment if any of the following criteria was present:

- kidney stone with complication(s): severe colic, anuria or severe infection of the urinary tract,
- diameter of calculus larger than 20mm,
- age under 18 years,
- pregnancy, lactation,
- allergy to terpenes or other components of Rowatinex.

9.3.3 Removal of patients from therapy or assessment

A patient was considered as having completed the study when he/she completed the Week 14 visit. If a patient discontinued at any time after entering the study, the investigator had to make every effort to see the patient, to complete the discontinuation form, and to make him return the study medication (Section 3.4.1, Schedule of Assessments).

9.3.3.1 Premature termination for individuals (dropout)

Each patient could revoke his consent to participate in the present clinical trial at any time and without giving reasons and without incurring any disadvantages as far as his continued or future medical care by the investigator was concerned. The time of dropping out, the reasons for doing so to the extent known, and the results available up to that time had to be recorded.

If an exclusion criterion occured during the clinical trial or the investigating physician assessed that the continued participation of the patient was not justifiable for other reasons, the trial should have been discontinued for this patient. The date and reason for termination as well as the results available up to that time had to be recorded in the case report form. In addition, the attempt to carry out a final medical examination had to be made definitely.

Additional reasons for a premature termination could be:

- Intolerable adverse events;
- Lack of patient compliance;
- Revocation of consent;
- Serious protocol violation.

If a patient was eliminated from the study because of an adverse event, for some reasonable time afterwards and perhaps even after the end of the study, the further course or outcome and the causal connection with the trial medication had to be clarified. If the patient did not appear at the planned follow-up examination, the reason had to be ascertained by the investigating physician as far as possible.

Rowa Pharmaceutical Ltd. was reserving the right to exclude individual patients from further participation on the grounds of serious or repeated protocol violations, because of administrative concerns, or for other reasons.

If it had been necessary to prematurely terminate the study for a patient, appropriate measures had to be taken to safeguard the patient's interests and health-related well-being as far as possible.

Patients, who terminated the study prematurely, e.g. due to withdrawal of informed consent, had to be treated in accordance to the decision of the physician in case of an ongoing necessity of an alternative therapy.

Drop-outs were not replaced.

The reason for any early discontinuation should be indicated on the CRF form. The primary reason for a premature discontinuation should be selected from the following standard categories of early termination:

- Adverse Event (Adverse Reaction): A clinical or laboratory event occurred during the trial that in the medical judgement of the investigator for the best interest of the patient is a reason for discontinuation. This included serious and non-serious adverse events regardless of relation to study medication.
- Death: The patient died.
- Withdrawal of Consent: The patient desired to withdraw from further participation in the study in the absence of a medical need to withdraw as determined by the investigator.
- Protocol Violation: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g. drug non-compliance, failure to return for defined number of visits). The violation necessitated premature termination from the study.
- Lost to follow-up: The patient stopped coming for visits and the study personnel was unable to contact the patient.
- Other: The patient was terminated for a reason other than those listed above, such as theft or loss of study drugs, or termination of study by the sponsor.

9.3.3.2 Premature termination of the entire trial

The entire trial could be interrupted or prematurely ended by the director of the clinical trial in consultation with the project co-ordinator at Rowa Pharmaceutical Ltd. after carefully considering the existing benefits and risks. The study was not terminated prematurely.

9.4 Treatments

9.4.1 Treatments administered

The administration of Rowatinex or Placebo was to be started at the first day of the trial five hours after ESWL in the morning. Patients were instructed to take 2.5 litres liquid to achieve standard hydration.

Patients were instructed to take 2 capsules 3 times daily before meals.

Should a patient have forgotten one dose, (s)he was instructed not to take this dose at a later time, but to miss the dose altogether. Patients were instructed to record dates of missed doses.

9.4.2 Identity of investigational product(s)

Investigational product

Trade name:	Rowatinex capsules
Code name:	Rowatinex
Galenic form:	capsules
Active ingredient:	Pinene (α+β) 31.0 mg, Camphene 15.0 mg, Cineol 3.0 mg, Fenchone 4.0 mg, Borneol 10.0 mg, Anethol 4.0 mg
Other ingredients:	Olive Oil 36.0 mg
Dose:	3 x 2 capsules per day before meals
Dosing schedule:	see above
Route of administration:	orally
Batch No.:	5084C-14, 5789C-15, 5793C-16
Manufacturer:	Rowa Pharmaceuticals Ltd., Newton, Bantry, Co. Cork, Ireland

Comparator

Trade name:	n.a.
Code name:	Placebo
Galenic form:	capsules
Active ingredient:	n.a.: placebo
Other ingredients:	n.a.
Dose:	3 x 2 capsules per day before meals
Dosing schedule:	see above
Route of administration:	orally
Batch No.:	4622C-5, 5851C-2, 5815C-3
Manufacturer:	Rowa Pharmaceuticals Ltd, Newton, Bantry, Co. Cork Ireland

The IMP is also available as medicinal product in Hungary since 1998 (Registration-No.: OGYI-T4912).

9.4.3 Method of assigning patients to treatment groups

The assigning of treatment group to a patient was done by randomization. Three randomization lists had been generated in January 2003, October 2005 and November 2005. On all occasions a patient treatment number list was generated with the appropriate numbers of patients listed (i.e., patient nr. 1-200 in January 2003, 201-250 in October 2005 and 251-300 in November 2005). Using the random number function of a Sharp Scientific Calculator (model

EL-531LH in January 2003 and model EL-531RH in October and November 2005) a random number was assigned to each patient treatment number. Within this centralized randomization procedure all patients were consecutively allocated to treatments across the sites. It had previously been decided that if the randomly assigned number was odd, the treatment for that patient would be Rowatinex; if the randomly assigned number was even, the treatment for that patient would be placebo.

HungaroTrial CRO received all medication and supplied centres with appropriate amounts (according to patient inclusion estimates) of the IMP. Each centre supplied the IMPs consecutively (lower number first).

So-called "emergency envelopes" were available for every centre. Inside the envelopes was the identification of the trial drug used for the individual patient. If in cases of serious or severe adverse events the identification of the trial drug was essential for adequate treatment of the patients, the envelope belonging to the affected patient could be opened by the investigator. Reason for and date of opening should be noted on the envelope and signed by the investigator and the project coordinator at Rowa Pharmaceuticals Ltd. should be informed. Each emergency envelope that was handed over to the investigator should be returned to the sponsor after completion of the study. No envelopes were opened during the study.

9.4.4 Selection of dose in the study

No dose change was foreseen in the study.

9.4.5 Selection and timing of dose for each patient

The assignment of dose regimen was according to the randomization plan.

9.4.6 Blinding

After determination of the therapy group for an individual patient from the central randomization procedure the centre received the selected patient number from the randomization head office by fax. The patient number consisted of a 4-digit code. Each centre had received active drug and placebo medication in advance which was labelled with medication numbers (e.g. 101-124). The allocation of the patient number was based on the result of randomization and was not depending on the date of inclusion. This procedure ensured the blinding of the investigator although the trial medication was stored in the centre.

The randomization list was produced by ROWA Pharmaceuticals Ltd., Bantry, Ireland using the Sharp Scientific Calculator (EL-531LH and EL-531RH).

9.4.7 Prior and concomitant therapy

All significant illnesses that the patient has experienced within three months of screening should be documented. Illnesses present when informed consent was given were regarded as concomitant illnesses. Illnesses first occurring during the course of the study and/or worsening of existing illnesses during the study were to be documented as adverse events in the CRF.

9.4.7.1 Concomitant treatment of the study indication

No other concomitant treatment of residual stones after ESWL was foreseen and permitted. If necessary, additional ESWL or surgeries should be reported in the CRF.

The analgesics used for pain therapy and the corresponding doses were to be recorded as well. Usual medications were Mometazine (Metamizol) tablets 500 mg or Drotaverine HCl 40 mg injection or tablets.

9.4.7.2 Permitted and prohibited other concomitant medication

Permitted concomitant treatment

No other therapy or medication was prohibited by the protocol. All necessary concomitant medication should be reported on the CRF.

9.4.8 Treatment compliance

Patients were instructed to return all used and unused medication boxes and blisters at each visit to allow assessment of compliance by capsule count.

Non-compliance is defined as taking less than 80% or more than 120% of study medication during any outpatient evaluation period (visit to visit). Discontinuation for non-compliance was at the investigator's discretion and had to be noted in the CRF.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and safety measurements assessed and flowchart

The procedures to be performed throughout the study are outlined in the Schedule of Assessments shown in Table 9-1 below.

Table 9-1: Study flowchart

Schedule of Assessments							
Assessment	Baseli-neScreen	Treatment Period					Follow-up
	Day 0	Day 1	Week 1	Week 4	Week 8	Week 12	Week 14
	V-S	V-1	V-2	V-3	V-4	V-5	V-6
Informed Consent	X						
Inclusion/Exclusion	X						
Medical History	X						
Physical Examination	X	X	X	X	X	X	X
Stone data	X	X	X	X	X	X	X
ESWL		X					
IVP	X						
US	X	X	X	X	X	X	X
Laboratory Tests	X					X	X
KUB	X	X		X	X	X	X
Pregnancy test	X						X
Stone elimination		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Study Drug Dispensing		X		X	X		
Study Drug Return/Compliance			X	X	X	X	

Screening examination (V-S)

At the entrance examination the patients were screened with respect to the inclusion and exclusion criteria. Every patient who fulfilled the selection criteria and gave her or his written informed consent for the participation in this clinical trial after thorough information by the investigator was included in the study.

During baseline examination the following demographic data were documented:

- initials
- gender
- date of birth.

Before the start of ESWL the case history was evaluated and clinical examination was performed. The following parameters had to be documented:

- Clinical examination including:
  - Height, weight

- Blood pressure, heart rate
- Physical examination according to the body system organ classes

- Laboratory examination including
  - Hematology (RBC, WBC, Hgb, Htc, platelet count, prothrombin)
  - Serum chemistry (calcium, phosphate, blood glucose, uric acid, bilirubin, creatinin, ALP, SGOT, SGPT)
  - Urine analysis (pH, WBC, RBC, urine culture)
  - pregnancy test
- Chemical composition of previous stone(s).

As parameters of previous therapy the following parameters were determined:

- Treated stone data
  - side
  - position
  - size
- ESWL data
  - intensity
  - number of SW's
  - anaesthesy data (if necessary).

Control visits (V-1, V-2, ..., V-5) during treatment phase

The control visits took place at the first day after ESWL (V-1) and additionally at Week 1, 4, 8, and 12 after ESWL.

During the control visits the following parameters were determined:

- vital signs (blood pressure, heart rate, body temperature)
- sensitivity of kidney area
- measurement of stone parameter
  - ultrasound (existence of echodens area, number of stones, size of largest stone)
  - dilatation of stone in the urinary tract (existence, size)
  - native kidney image
  - position, size of stone
- pain assessment
- necessity and reason for surgical interventions
- ESWL complications
- other than ESWL complications
- issued and returned study medication.

At V-5 an additional laboratory examination similar to that at screening was performed.

In case of adverse events or use of concomitant medication these events were reported on separate documents.

Follow-up visit (V-6)

A follow-up visit was planned at Week 14 after ESWL with evaluation of the the same parameters as at V-5 (Week 12).

Finishing therapy

At the end of the therapy an additional sheet had to be filled out indicating the patient's completion of the trial according to the protocol. If the patient was not completing the trial according to the protocol, the last ingestion of the study medication and reasons of premature discontinuation had to be documented.

Adverse events / Concomitant therapy

Adverse events and relevant concomitant therapies should be documented in separate documents. Information related to AEs were

- Start date / end date
- Severity
- Relation to study medication
- Seriousness
- Effect on further treatment.

Information related to concomitant medications were

- Start date / end date
- Medication
- Daily dose.

9.5.1.1 Assessment of efficacy

Primary efficacy:

- Proportion of patients with "stone-free status of patients after 3 months": this variable was derived from measurement of the target stone.
- Proportion of patients requiring surgical intervention due to complications or residual stones.

Secondary efficacy:

- Time to stone-free status
- Efficacy of pain-control (VAS), change from Visit 1 to final assessment.

- Pain-control as assessed by responder (50% reduce of pain against baseline) and remitter (pain = 0) rate
- Rate of clinically insignificant and clinically significant residual stones
- Frequency of complications requiring surgery
- Frequency of ESWL complications including clinical symptoms
- Subgroup analysis of patients stratified by size and position of treated stone

9.5.1.2 Assessment of safety

According to the visit schedule described above (Table 9-1), the safety variables were assessed and recorded by the following methods:

Adverse events

In accordance to clinical safety data management (ICH E 2a, CPMP/ICH/377/95) adverse events (AE) are all events that occur within a clinical trial. The term AE does not imply automatically a relation to the treatment that is the objective of the trial. Adverse events could be pathological laboratory values, diseases, or symptoms.

All adverse events were documented in a special adverse event record form. The documentation included the duration (date of start and end or continuation), severity (mild, moderate, severe), seriousness (no, yes), the possible causal relationship to the study treatment (no presumed relationship, unlikely related, possible, probably related, relationship assured) as well as the influence on the further course of the study and the need for a specific therapy.

Serious adverse events

An AE that met one or more of the following criteria was classified as serious (SAE):
- Event led to death.
- Event was life-threatening (i.e., at immediate risk of death).
- Event required in-patient hospitalization or prolongation of existing hospitalization.
- Event was persistent or entailed significant disability/incapacity.
- Event was a congenital anomaly/birth defect.

Important AEs that did not result in death, were not life-threatening, or did not require hospitalization could have been considered as serious when, based upon appropriate medical judgement, they might have jeopardized the patient or required medical or surgical intervention to prevented one of the outcomes listed above.

Serious also included any other event that the investigator or the sponsor judged to be serious or which was defined as serious by the regulatory agency.

These events had to be recorded on the SAE-CRF-record form that had to be sent by HungaroTrial CRO within 24 hours to the sponsor. If necessary, this first report was to be followed

by a second report that had to contain any final information and results of further investigation that could be helpful to evaluate a possible connection between the treatment and the SAE.

Vital signs

The following vital signs were monitored as safety parameters:
- Blood pressure, systolic and diastolic (SBP, DBP),
- Heart rate,
- Body temperature,

Laboratory assessments

Hematology, clinical chemistry, and urine analysis was performed at local laboratories at the study sites by means of established methods. Normal ranges as well as quality assurance certificates were available to the sponsor prior to study start.

9.5.2 Appropriateness of measurements

Efficacy evaluation was done by assessing the existence, position and size of residual stone after ESWL from ultrasound methods, intravenous pyelography, and KUB X-Ray investigations. All these methods together should give a valid assessment of residual stone status. As a second measure of the efficacy of ESWL plus Rowatinex treatment, the number and reason for surgical interventions due to complications were evaluated.

Patients' subjective assessment of strongest pain since the last visit on a visual analog scale should give adequate information for concomitant pain experience.

With the methodology of this trial, the clinically most relevant features of nephrolitiasis and its midterm outcome could be assessed.

Additional complications were measured by frequencies of frequent adverse events like headache or vomiting for a further safety comparison between Rowatinex and placebo.

9.5.3 Primary efficacy variable(s)

The primary analysis was performed comparing treatments with respect to the proportion of patients with stone-free status or with no surgical interventions within 12 weeks after start of treatment.

"Time to stone-free status during the study" was a secondary efficacy variable which was expected to support the primary efficacy analysis on the rate of stone-free patients.

While the first primary efficacy measures, stone-free patients, emphasize the success of the patients' treatment, the second primary efficacy measure is related more closely to complicative treatment by analyzing complications which occurred after randomization.

9.5.4 Drug concentration measurements

Drug concentration measurements were not foreseen in the Protocol.

9.6 Quality Assurance

9.6.1 Deviations or changes to the protocol

All aspects of the protocol were to be complied with during the trial period. In case changes became necessary, they were to be discussed without delay by the principle investigator, the monitor, and the sponsor and required a written protocol amendment before implementation. The protocol amendment should contain a detailed justification of the modification. Additionally, the amendment required approval by the Ethics Committee. A copy of the written approval of the IRB/IEC, which became part of the protocol, had to be forwarded to the sponsor.

Three amendments to the study protocol were introduced during the course of the study. In Amendment 1, dated 07 Jun 2004, besides nephrolithiasis, also patients with ureter stones after ESWL were permitted to participate in the trial. Amendment 2, dated 15 Feb 2005, introduced an interim analysis which became necessary to meet the timelines set by the regulatory authorities to provide further data on Rowatinex in the treatment of patients following ESWL. In addition, the statistical analysis of the study was described in greater detail. In Amendment 3, dated 17 Oct 2005, the final sample size as calculated with the data from the interim analysis was increased from 160 to 222 patients.

All three amendments were approved by the responsible ethic committees before the proposed changes of the protocol were implemented.

9.6.2 Methods to standardize performance

During two investigator meetings (dated 14 Sep 2004 and 24 November 2004), investigators and site personnel were initiated to the background, rationale, and organizational aspects of the trial. The investigator received further instruction on how to fill out the Case Report Forms (CRFs) and the included Adverse Event Report Form (AER). These procedures were repeated during the study iniation visits at each site.

Local laboratories were responsible for all assays stipulated by the study protocol. Normal ranges and quality assurance procedures were available for each local laboratory (Appendix 16.1.9).

9.6.3 Monitoring

It was in the investigator's responsibility to ensure that the study was conducted according to the agreed protocol as well as to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Furthermore, it was in the responsibility of the investigator to assure that all relevant data such as patient history, concomitant diseases and medication, date of study inclusion, date of study visits, results of examinations, and adverse events were properly documented in the patient's original files.

The investigator bore responsibility that all persons involved in the trial were instructed concerning their tasks.

The study was monitored in accordance with the Standard Operating Procedures (SOPs) of Hungarotrial (Budapest) and the sponsor by native Hungarian speaking clinical research associates, paying special respect to the guidelines of Good Clinical Practice (GCP).

The investigator agreed to allow the monitor or an employee of the quality assurance unit of the sponsor, to personally ascertain the correct implementation and documentation of the study during scheduled visits (approximately every 4 – 8 weeks, dependent on the recruitment rate). It was the purpose of the trial monitoring to verify that:

- The rights and well-being of human subjects were protected.
- The reported trial data were accurate, complete, and verifiable from source documents.
- The conduct of the trial was in compliance with the currently approved protocol, with GCP, and with the applicable regulatory requirements.

For this purpose, it was necessary to compare the data entered to the CRF with data from the medical records, etc. Especially, the availability of the properly signed and dated informed consent form was checked. No information in the medical records about the identity of the patients left the study centre.

The exact extent of the monitoring and source data verification was fixed in a Trial Management Plan.

9.6.4 Audit and inspections

As part of the contract, the principle investigator and each investigator agreed to allow an auditor appointed by the sponsor as well as representatives of relevant authorities and the Eth-

ics Committees to verify by a study site audit that implementation and documentation were in accordance with the protocol, Good Clinical Practice, and the applicable law.

The auditor/representative was free to scrutinize all of the essential documents and to check the correspondence of a random sample of data entered to the CRFs with the source data of clinical records. Therefore, the investigator had to provide direct access to source data/documents and to the locations where trial-related activities took place (e.g., laboratory, pharmacy).

Audits were performed at three sites (02: 25 May 2005; 03: 27 May 2005; 05: 02 Jun 2005). There were no critical findings which would have jeopardized the acceptability of the study and its data. Among a few significant findings which describe significant deviations from Good Clinical Practice or Standard Operation Procedures there was none which had an impact on the validity of the study data. In summary, the site audits did not reveal any critical impact of deviations from the protocol on the validity and acceptability of the study data.

9.6.5 Data handling

9.6.5.1 Documentation of data

Patient data collected on CRFs during the study were documented in an anonymous fashion, which means that the patient could only be identified by the patient number and by initials. If, as the one exception, it had been necessary to identify the patient for safety or regulatory reasons, both the sponsor (including CRO staff) and the investigator had been bound to keep this information confidential.

All data obtained during this study were raw data and to be entered by the investigator in the CRFs immediately. Details on how to complete the CRFs were explained to the investigator.

The following data had to be available as source data in the patients's medical records as kept by the investigator:

- Patient's consent to take part in this study (to be identified by study number, investigational drug, randomization number, and treatment period);
- Anamnestic data;
- Records of concomitant diseases/treatments and medication;
- Visit dates;
- Records of telephone contacts between investigator and patient;
- Application of study drug;
- Records of adverse events;
- Reason for premature discontinuation, if applicable.

The following data could be recorded directly on the CRFs (no prior written record) and were considered to be source data:

- Results of ultrasound;
- X-ray of kidney, ureter, and bladder (KUB);
- Reasons for surgical interventions;
- ESWL complications and other complications;
- CT of the abdomen with intravenously or orally contrasting;
- Vital signs;
- Application of study medication and patients' compliance.

As planned in the protocol, the CRF was written in Hungarian language. The CRF was made of non-carbon paper. The original pages were collected by the responsible monitor, and the bottom copy was retained by the investigator.

Entries to the CRF had to be made legibly, by use of a black ball-point pen.

If the investigator authorized other persons to make entries to the CRF, the names, positions, signatures, and initials of these designees were documented.

CRFs had to be filled in immediately after each examination. The completed CRFs were signed by the investigator and the authorized person, respectively, as named in the protocol.

A reasonable explanation was to be given by the investigator for all missing data.

Corrections to study documentation: If corrections were made to entries on the CRF by the investigator or designates, the words or figures had to be crossed out, leaving the initial entry legible. The correction had then to be dated, initialed, and explained, if necessary. Incorrect entries were not allowed to be covered with correcting fluid, to be obliterated, or to be made illegible however.

All patients who presented with the inclusion diagnosis and were screened by the investigator were to be recorded in a separate list (patient enrollment log).

Participation in the study was documented in the medical record. The investigator also kept a summary list to facilitate identification of the patients by the patient number (patient enrollment log). This list was intended for own use only and was not allowed to be seen by third persons, except for purposes of monitoring, auditing, or inspection by an authority.

9.6.5.2 Processing of data

Data entry and data management was performed according to SOP DM_001rev001 of the data management company Planimeter in Budapest, Hungary (www.planimeter.hu).

The original sheets of the CRFs were collected by the monitor during study site visits after Source Data Verification was performed and forwarded to data management of the sponsor. For reasons of security and verification, copies remained with the investigator.

A first quality check of the documented data was performed during the regular monitoring of the study. After receipt of the CRFs by the analyzing institute they were checked for documented adverse events in the first place, which were administered in a safety database and reported to the sponsor continuously.

All CRFs were checked for completeness, plausibility, and conformity with the GCP-requirements in the documentation (e.g. with respect to corrections). Corrections were made either by the use of Self Evident Correction Forms (SEC) by the Data Manager of Planimeter or by using Query Forms which had to be answered by the investigator. SECs and Queries were contents of the CRFs and a copy was forwarded to the centre for storage with the CRF.

A study specific database was set up using SAS, an FDA approved database system. Data from each CRF were entered to this database in an anonymized way. All data were entered twice by different persons using verify mode. Not identical data were corrected, while the correction was documented in an Audit Trail File. The database was closed after all CRF-data had been entered; this procedure was documented. This extensive document is available and might be added to the appendices, if required by the regulatory authority. The randomization code was opened only after the complete database had been received by the sponsor.

The database was sent to the CRO comprehending both MS Excel® files and database files. The data transfer between MS Excel® and the SAS™ data sets was performed by the DBMS-COPY conversion program.

The statistical package SAS™ for Windows, release 8.2, was used for statistical evaluation.

Data cleaning

During the initiation phase of the study a data management plan was developed in which the data handling was described in great detail. The data management plan included specifications for the consistency and plausibility checks. Based on these validation rules, automated (i.e., programmed) or manual data validation were performed. Obvious data errors were handled according to the respective rules, and query/correction sheets for unresolved queries were generated and sent to the study monitors for resolution with the investigator. Based on signed data corrections the database was updated accordingly.

All missing and/or spurious data were subject to data queries as specified above if they were not explained reasonably by the investigator. All CRF data was entered to the electronic database and was considered for analysis as specified in the Statistical Analysis Plan (SAP).

9.7 Statistical Methods planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans

9.7.1.1 Hypotheses

The target variables for the biometric analysis are completely listed in section 9.5.1. The biometrical analysis aimed to prove superiority of Rowatinex compared to placebo. This was done in a confirmatory way (a) with the criterion "rate of stone-free patients" and (b) the criterion "requiring surgical interventions due to complications or residual stones". The two objectives were defined as follows:

a) The achievement of stone-free status within 12 weeks after ESWL confirmed simultaneously by repeated X-ray (KUB) or ultrasound (US) or both methods. For the confirmatory analysis of the criterion "rate of patients who became stone-free within three months after start of treatment with study medication (dichotomous variable)" the last result under study medication was used. The one-sided null hypothesis of rates (i.e., equal or higher under Rowatinex)

$$H_{01}: \Pi_{Rowatinex} \geq \Pi_{Placebo}$$

under both treatment conditions was tested against the one-sided alternative hypothesis of the superiority of the Rowatinex medication compared to placebo

$$H_{11}: \Pi_{Rowatinex} > \Pi_{Placebo}$$

with Fisher's exact test for the analysis of fourfold tables.

b) The second objective "need for surgical interventions" was determined from the necessity of any such intervention during the study.

The hypothesis of an equal or higher rate of patients "requiring surgical interventions" under Rowatinex compared to placebo

$$H_{02}: \Pi_{Rowatinex} \geq \Pi_{Placebo}$$

was tested against the one-sided alternative hypothesis of a superiority of the Rowatinex medication against placebo

$$H_{12}: \Pi_{Rowatinex} > \Pi_{Placebo}$$

with Fisher's exact test for the analysis of fourfold tables. by a logistic regression model, fitting terms for treatment group and center, applied for proportion of pa-

tients with no surgical interventions within 12 weeks after start of treatment. The p-value of treatment effect from the logistic regression model was used.

The objectives of the statistical evaluations were assessed with a one-sided error probability of $\alpha = 0.025$. The two primary endpoints were ordered hierarchically within a closed test procedure: The first variable to be tested was the rate of stone-free patients; the second was the rate of patients with surgical interventions. Confirmatory analysis has to be stopped after the first comparison if the null hypothesis of equal rates of stone-free patients under both treatments could not be rejected.

According to the interim analysis the respective null hypotheses H_{01} and/or H_{02} were to be rejected if the respective product of both p-values from first and second part of the study did not exceed the level of $c_\alpha = 0.0038$ (see section 9.7.1.4).

Secondary Objectives

Secondary variables were analyzed in a descriptive manner both for the ITT and the PP populations.

The time to stone-free status within 12 weeks after ESWL was compared between the two treatments using the long-rank test.

Frequency of surgical interventions in general and by category was compared with a 2-sample Wilcoxon U-test or t-test, or by a Chi-Square contingency test, depending of the distribution of these events. In addition, ESWL complications (haematuria, fever, pyelonephritis, occlusion, haematoma) and clinical symptoms (headache, vertigo, nausea, vomiting, eruption) specified in the CRF were compared by binomial tests including 95% confidence intervals for differences in rates.

The number of clinically insignificant as well as clinically significant residual stones was compared. A clinically insignificant residual stone was defined by a stone size smaller than 4 mm without symptoms. A clinically significant residual stone was defined by a stone size smaller than 4 mm with symptoms. Descriptive frequency distributions were provided for the outcome categories of the assessment of residual stones (findings with ultrasound, native kidney image, position, and size of stone).

For pain assessment with the visual analogue scale (VAS), an ANCOVA (analysis of covariance) was performed for the changes from baseline to end of the final assessment with treatment group as the main factor, baseline as covariate, and center as a classification.

Additionally, a responder and remitter rate assessment was performed for the VAS pain score. A responder was defined as a subject with a decrease of 50% in VAS pain score at the final assessment (Week 12 assessment or assessment at the time of premature discontinuation as last available assessment) compared to baseline. A remitter was defined by a VAS pain

score = 0 at the final assessment. To compare the two treatment groups, Chi-Square tests (or Fisher's exact test) were performed per visit and at the endpoint, and p-values were provided for descriptive purposes only.

9.7.1.2 Analysis populations and eligibility procedure

Definition of analysis populations

The various types of patient population were distinguished by their progress in the clinical trial. Screened patients refer to patients who were examined at least once to determine qualifications for entry into the study. Qualified patients refer to the subset of screened patients who were enrolled into the study and satisfied inclusion/exclusion criteria. Randomized patients refer to those who were assigned a medication number and entered into the treatment period. Completed patients are those randomized patients who completed the full duration of the 12-week treatment and follow-up with normal termination of the trial.

The **safety-analyzable population (SAF)** consists of all randomized patients who have safety data after the first dose of study drug. Note that if a patient has no adverse event, this defines a safety statement.

The **intent-to-treat population (ITT)** consists of all randomized patients with at least one post-randomization (on-drug) efficacy evaluation. Patients, who were stone-free immediately after ESWL, were excluded from the ITT population and any other populations to evaluate efficacy. Those patients are listed with all available information.

The **per-protocol population (PP)** consists of all patients of the ITT population who completed the study without major protocol violations. Protocol deviations were defined prior to unblinding in two blind data review meetings and documented properly in a protocol of that meeting.

The primary efficacy-evaluable population for the primary efficacy analysis in this study was the ITT population. Additional analyses in the PP population were performed to corroborate the results from ITT analysis.

For an additional analysis of primary efficacy variables the following Completer Sets (CS) were derived.

The **intent-to-treat population completer set (ITT-CS)** consists of all patients from the ITT set finishing the treatment according to the protocol.

The **per-protocol population completer set (PP-CS)** consists of all patients from the PP set finishing the treatment according to the protocol.

9.7.1.3 Subgroup analysis

In a subgroup analysis, patients with initial residual stones of size ≤ 8 mm and > 8 mm were compared between the two treatment groups with respect to the primary efficacy variables in an exploratory manner. In additional subgroup analyses, the two primary efficacy endpoints were stratified according to position of stone prior to ESWL (upper, lower, middle calix, pyelum-PU passage for left and right side). These supportive analyses were performed both with the ITT and the PP population.

9.7.1.4 Interim analysis

Due to a request of the Competent Authorities (BfArM, Germany) for new data on the efficacy of Rowatinex an interim analysis was planned with all data from all patients who had completed the trial until 23 MAY 2005. This interim analysis became necessary since the recruitment of patients into the trial was slower than expected.

The planning of the adaptive interim analysis was such that the following possibilities were open for decision depending on its results.

- The trial should be terminated after the interim analysis if H_0 of equal efficacy could be rejected for both primary efficacy measures. In this case, clinical superiority of Rowatinex compared to placebo is demonstrated.
  If only the first H_0 could be rejected (rate of stone-free patients) the trial should also be terminated after the interim analysis.
- The trial should be terminated after the interim analysis if H_0 was accepted for both primary efficacy variables. In this case, the superiority of Rowatinex over placebo was not demonstrated.
- The trial should be continued with a 2nd part after the interim analysis, if $0.0102 < p < 0.5$ for both primary efficacy variables or at least for the first primary efficacy variable.

Within the interim analysis, as boundary for accepting the null hypotheses a value of a one-sided $\alpha_0 = 0.30$ was defined. To ensure an overall error probability of $\alpha = 0.025$ (one-sided in each of the both hypotheses) the critical boundaries for the rejection of the null hypotheses were set to $\alpha_1 = 0.0102$ for the interim analysis and $c_\alpha = 0.0038$ for the product of one-sided p-values in the final analysis, respectively. Critical values $\alpha_1 = 0.0102$ and $c_\alpha = 0.0038$ were evaluated according to Fisher's combination test for two stage adaptive design (see e.g. Bauer & Köhne, 1994) and checked by the ADDPLAN®, Release 3.0 software.

With the following hierarchical decision strategy for the multiple test problem a multiple type I error probability of $\alpha = 0.025$ was controlled for the one-sided hypotheses H_{01} and H_{02}.

Notations:

p_{11} or p_{12}: p-value of the 1st part of the study associated with the null hypothesis H_{01} or H_{02}

p_{21} or p_{22}: p-value of the 2nd part of the study associated with the null hypothesis H_{01} or H_{02}. Only patients who were randomized in the 2nd part of the trial were used for calculating p_2 and $p_2(\delta)$.

Decision strategy:

- The trial should end after the interim analysis with rejection of H_{01}, if $p_{11} \leq \alpha_1 = 0.0102$. In this case, by maintaining a multiple level $\alpha = 0.025$, additionally the null hypothesis H_{02} could be evaluated and rejected if $p_{12} \leq \alpha_1 = 0.0102$.
- The trial should end after the interim analysis without rejection of H_{01}, if $p_{11} \geq \alpha_0 = 0.5$. In this case, also the null hypothesis H_{02} was to be maintained.
- The trial could be continued with a 2nd part after the interim analysis, if $0.0102 < p_{11} < 0.5$ and if $0.0102 < p_{12} < 0.5$. The null hypothesis H_{01} can be rejected within the final analysis, if $p_{11} \cdot p_{12} \leq 0.0038$. In this case, by maintaining a multiple level $\alpha = 0.025$, additionally the null hypothesis H_{02} can be evaluated and rejected if $p_{21} \cdot p_{22} \leq 0.0038$.

The following measures were applied to keep the study blinded:

(1) The only person who had the full information on the patients' treatments available was the medical expert.
(2) The random code list containing the treatments of the individual patients was sent to the medical expert. He selected those patients who were included into the interim analysis, coded the treatments as "A" and "B", and sent the list with patient numbers and treatments (A or B) to the responsible statistician. The list was provided after the data base for the interim analysis was frozen and a copy was sent to the medical expert.
(3) The outcome of the statistical interim analysis was sent in form of a statistical report including tables and listings to the medical expert. No other person involved in the conduct of the study must have had access to the results of the interim analysis. At the statistical institution, the code list and the outcome of the statistical analysis including the statistical report was taken from the computer system and stored strictly confidentially in a secured place.
(4) The decisions based on the above decision strategy were made either by the expert himself if the null hypotheses could be rejected or must be maintained or in cooperation with the statistician to calculate the sample size for the second part of the study. In the latter case, the only information given to the study team was to continue the trial with the calculated number of patients. However, no information on specific results of the interim analysis was made available to any person of the study team.

(5) The medical expert reported the results of the interim analysis directly to the regulatory authorities.

9.7.2 Statistical methods to be employed

The data documented in the CRF regarding the sample description (demo- and biographic data, medical history, results of the physical examination), efficacy as well as safety are presented in tables. For continuous variables the arithmetic mean, standard deviation, median, minimum and maximum were calculated and the respectively available sample size were stated per variable. Categorical variables are presented in frequencies tables (absolute and percentage). Free verbal entries of the investigators (comments, concomitant diseases, concomitant medication, and adverse events) were summarized. In case it was necessary for the clarity of the results and allowed by the kind of data, the results are presented graphically.

In case of continuous variables, descriptive comparisons were performed by using the t-test for independent samples, the Wilcoxon-rank-sum-U-test or the χ^2-test. Categorical variables were analyzed with χ^2-test or Fisher's exact tests.

Exploratory Target Parameters, Additional Parameters

The exploratory objectives listed in section 9.5.1 (secondary efficacy) were evaluated with respect to differences between the two treatment arms using 2-sample-tests, frequency-analysis, analysis of covariance, and logistic regression. Aside from endpoint analyses all available data were evaluated per assessment.

9.7.2.1 Demographic and other baseline characteristics

The following variables were reported in a descriptive manner to describe the baseline status of the patients:

- Gender and age
- Medical history
- Disease characteristics
    - affected side with treated stones
    - position of treated stones
    - size of treated stones
    - chemical composition of previous stones
- Treatment characteristics
    - number of shock waves (ESWL)
    - intensity of shock waves

No formal testing for treatment group comparisons was performed.

9.7.2.2 Study drug

Compliance of patients was evaluated at number of used tablets (dispensed minus returned) related to number of tablets that should have been used and analyzed by descriptive statistics. Patients with treatment compliance smaller than 80% were reported explicitly.

9.7.2.3 Efficacy analysis

Tests by the means of confirmatory statistics were performed for the objectives based on the boundaries for the interim analysis. Transition probabilities of the tests used are explicitly given, however, p-values <.0001, if any, were not rendered more precisely.

Primary efficacy variable(s)

The rates of "stone-free" patients at study end were compared with a chi²-test. Note: The "surgical interventions due to complications" were also planned to be analyzed with a chi²-test. (This analysis was not done because of the low number of patients with surgical interventions.) According to the Fisher-combination test strategy for the analysis of a second part trial after an interim analysis (see e.g. Bauer & Köhne, 1994) the following critical values were used.

To protect type I error probability by multiple testing, the two primary endpoints were ordered hierarchically within a closed test procedure: The first variable to be tested was the rate of stone-free patients; the second was the rate of patients with surgical interventions. Confirmatory analysis had to be stopped after the first comparison if the null hypothesis of equal time to stone-free status of patients under both treatments could not be rejected.

Within the interim analysis, as boundary for accepting the null hypotheses a value of a one-sided $\alpha_0 = 0.50$ was defined. To ensure an overall error probability of $\alpha = 0.025$ (one-sided in each of both hypotheses) the critical boundaries for the rejection of the null hypotheses were set to $\alpha_1 = 0.0102$ for the interim analysis and $c_\alpha = 0.0038$ for the product of one-sided p-values in the final analysis, respectively.

Secondary efficacy and exploratory target variables

Survival-analysis was performed with the Logrank-test for "time to stone-free".

Analysis of covariance for the pain VAS was used to identify treatment effects with adjustment to baseline values. Logistic regression with treatment group and center as factors was used to assess the treatment by center effects regarding the rate of stone-free patients.

Other secondary objectives were evaluated with respect to differences between the two treatment arms using appropriate 2-sample-tests and frequency-analysis. Aside from end-point-analyses all available data were evaluated per assessment (visit).

9.7.2.4 Safety analysis

Listings and tables of all variables of the safety evaluation were provided for the safety population. Tolerability and safety of both treatment arms were described using the following criteria.

Adverse events

Safety assessment was mainly based on analysis of adverse events. An adverse event (AE) was any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event was not considered to be treatment-related. Adverse events were coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it was a serious AE (SAE), were indicated. An adverse event related to study drug was defined as one considered by the investigator to have a suspected relationship with the study drug (suspected = possibly, probably or highly probably related to the application of the study treatment). The adverse events were summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term was used for a given patient. Summary tables of adverse events by treatment and severity were provided. Adverse event analysis included new or, compared to baseline, worsened clinically relevant findings in the physical examination or in laboratory or vital signs assessments.

Multiple occurrences of the same AE or SAE in the same patient were counted only once, using the worst severity and drug relationship. SAEs were reported by narratives including relevant medical information.

Suspected unexpected serious adverse reactions (SUSARs) are discussed in the CSR. SUSARs are defined as those SAEs with a suspected relationship to study drug which are not listed in the CCSI.

In detail, the following calculations for AEs were performed and tables generated (SAEs are included into this analysis):

1. Number of patients with at least one AE (basis: all AEs reported including multiple counts) by body system and preferred term
2. Number of patients with suspected drug-related adverse events, summarized by body system and preferred term

3. Number of patients with adverse events, summarized by body system, preferred term, and maximum severity
4. Number of adverse events by worst severity and worst drug relationship
5. Frequency distribution of preferred terms and body systems according to MedDRA of all AEs (without multiple counts)

Besides absolute counts of AEs, relative frequencies per AE were reported with reference to all patients treated with at least one dose of the study medication per treatment and total (safety population).

For patients who discontinued from the trial without being treated with study medication, only a listing of AEs was provided if such events were documented in the CRF.

A listing of AEs was generated, sorted by center and patient. The listing includes the following variables: center, patient ID, treatment and analysis population, adverse event (reported term, preferred term, body system), duration (start- and end-date), course of AE, severity, relationship assessment, indication of SAE, and action taken.

Deaths, other serious adverse events, and adverse events having caused premature discontinuation from the study were additionally described in narratives which include demographic data, any available medical information, treatment(s), a full description of the event including any related information, and the outcome of the event.

Laboratory assessment

Counting the number of clinically notable laboratory assessments that fell outside of predetermined ranges (abnormalities) was the main way to analyze laboratory measurements. However, in the CRF detailed information on laboratory data was only reported in the event of abnormal values according to the local laboratory normal values per parameter. Therefore, a group statistical analysis of laboratory data (e.g., changes from baseline) was not considered to make sense.

Laboratory data were summarized by shift tables which included the categories "normal" and "abnormal". The relative and absolute numbers of patients with laboratory abnormalities were presented. In data listings the abnormal laboratory values were reported, if possible in SI units.

Vital signs

Counting the number of clinically notable vital signs values that fell outside of pre-determined ranges (abnormalities) was the main way to analyze vital signs measurements. In addition, changes between any post-baseline assessments compared to baseline were summarized by descriptive statistics.

Clinically notable values were identified according to the following criteria based on the FDA's "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates" (Revised 2-APR-87) provided by the FDA Division of Neuropharmacological Drug Products:

Table 9-2: Clinically notable vital signs abnormalities

Variable			Change Relative to Baseline
Heart Rate	≥ 120 bpm	and an	Increase of ≥ 15 bpm
	≤ 50 bpm	and a	Decrease of ≥ 15 bpm
Systolic BP	≥ 180 mmHg	and an	Increase of ≥ 20 mmHg
	≤ 90 mmHg	and a	Decrease of ≥ 20 mmHg
Diastolic BP	≥ 105 mmHg	and an	Increase of ≥ 15 mmHg
	≤ 50 mmHg	and a	Decrease of ≥ 15 mmHg
Weight			Change of ≥ 7%

The relative and absolute numbers of patients with notable abnormalities were presented. In data listings notable values were flagged.

New or worsened findings in any post-baseline examination compared to baseline were reported additionally as AEs in the CRF, if clinically relevant.

The Body Mass Index (BMI) was calculated as follows: (Body weight in kg) / (body height in m)^2. The respective unit of the BMI is kg/m^2.

Body temperature was tabulated by descriptive statistics.

9.7.3 Determination of sample size

One hundred and sixty (160) patients were planned to be recruited to participate in this study. This sample size was expected to provide 80% power to detect 23% difference in the proportion of patients with stone-free status at Week 12 between treatment groups with a one-sided 2.5% probability of Type I error rate while supposing 80% success rate in the Rowatinex group.

Sample Size Considerations

The sample size for the 1st part of the study was determined by the current recruitment status and included all patients who are randomized to the two study treatments until 28 FEB 2005. A sample size of more than 100 patients was expected for the interim analysis.

Due to the relatively high rate of patients lost to follow up, observed during the interim analysis, the planned sample size to be recruited in the study was increased to 222 patients.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the planned analysis

The concept of statistical analysis of the data of this trial has been considerably changed in Amendment N° 2 (FEB 2005) with the main modification of introducing an interim analysis. The Statistical Analysis Plan for the interim analysis contains the proposal as outlined in that amendment.

The main changes concerned the introduction of an administrative interim analysis which was introduced to keep the timelines of regulatory authorities. Instead of a sequential procedure, an adaptive approach was chosen, taking the unpredictable expected response rates with regard to the primary efficacy outcome measures into account.

The Final Study Report incorporates the results from the interim analysis. Additionally the planned sample size in the protocol was changed after the interim analysis by Amendment N° 3 (see also section 9.7.3).

10 STUDY PATIENTS

The total duration of the study was about 1254 days or 3.43 years. The study keystones are given in Table 10-1.

Table 10-1: Study duration (All Patients)

First patient First visit	26/06/2003
First patient Last visit	29/07/2003
Last patient First visit	11/09/2006
Last patient Last visit	01/12/2006
total study duration (days)	1254

Reference: Appendix 16.2, Table 1.0

10.1 Disposition of Patients

A total of 223 patients was enrolled into the study in six study sites, 222 of those were randomized and treated since one patient (number 200) withdrew informed consent prior to start of treatment with study medication (Table 10-2).

A rate of 8.1% (n=18) of all patients in the SAF population was excluded from efficacy analysis; 6.8% (n=15) were excluded from efficacy analysis because they were stone-free already at Visit 1, immediately after ESWL. Further 28 patients (12.6%) discontinued from the trial because they became stone-free during the course of the trial. Fourteen patients (12.7%) receiving Placebo and 20 patients (17.9%) receiving Rowatinex did not complete the study for other reasons than stone-free status, mainly due to loss to follow-up (see Table 10-3). In this study, loss to follow-up included both patients who were lost to non-compliance but also patients who were symptom-free and considered to stop treatment by their own. However, there is no information available on individual patients.

Table 10-2: Disposition of patients: overview (All Patients)

	No medication	Placebo	Rowatinex	Total
Enrolled patients	1	110 (100.0)	112 (100.0)	223 (100.0)
Randomized/Exposed patients	--	110 (100.0)	112 (100.0)	222 (99.6)
Stone-free patients at V-1	--	10 (9.1)	5 (4.5)	15 (6.7)
Completers	--	81 (73.6)	72 (64.3)	153 (68.6)
Ongoing (Follow-Up)	--	1 (0.9)	--	1 (0.5)
Non-Completers	1	28 (25.5)	40 (35.7)	69 (30.9)

Remarks: Number and row percent (in parentheses) of patients in each group from total analysis set.
Completers are patients who were treated for 14 weeks..
Reference: Appendix 16.2, Table 1.1

Reasons for discontinuation are given in Table 10-3. Besides achieving a stone-free status immediately after ESWL or during the study there were 22 patients lost to follow-up due to other reasons with no further specification. Additonally, there were three patients under Rowatinex reporting different other reasons. One of those patients was missed at V-5 and V-6; the other two patients gave the following reasons:

- Repeated ESWL, followed by percutaneous nephrolithotomy (PCNL)
- Repeated ESWLs due to occlusion.

Table 10-3: Reasons for discontinuation (SAF)

	Placebo	Rowatinex	Total
	N = 110	**N = 112**	**N = 222**
Completers	81 (73.6)	72 (64.3)	153 (68.9)
Ongoing (follow-up)	1 (0.9)	--	1 (0.5)
Non-Completers	28 (25.5)	40 (35.7)	68 (30.6)
Adverse event(s)	--	3 (2.7)	3 (1.4)
Withdrawal of consent	2 (1.8)	4 (3.6)	6 (2.7)
Lost to follow-up:	26 (23.6)	30 (26.8)	56 (25.2)
stone-free after V-1	11 (10.0)	17 (15.2)	28 (12.6)
other	12 (10.9)	10 (8.9)	22 (9.9)
Other reasons	--	3 (2.7)	3 (1.4)

Remarks: Number and row percent (in parentheses) of patients in each treatment group and total set.
Multiple counts by reasons for non-completion.
Reference: Appendix 16.2, Table 2.2

10.2 Protocol Deviations

Protocol deviations recorded for this study included subjects who entered the study even though they did not strictly meet all selection criteria and subjects who deviated from the pro-

tocol after the start of treatment with study drugs. A detailed list of all patients with premature discontinuation is given in Appendix 16.4, Listing 13.

11 EFFICACY EVALUATION

11.1 Data Sets Analyzed

For a detailed definition of the data sets see the Blind Review Protocol (21 Nov 2006). The safety population (SAF) consists of 222 randomized patients (see Table 11-1) who were treated with at least one dose of study medication. There were 18 patients excluded from ITT, 15 of them were already stone-free at V-1. For one of the remaining three patients (06-188) no post-baseline efficacy values were available, this patient discontinued the study on Day 1. Two other patients were also excluded from ITT (01-38 and 02-141) because there were no post-ESWL efficacy values available. These 18 patients were not considered for evaluation of efficacy.

In the remaining ITT population consisting of 204 patients, 98 patients (89.1% of this group in the Safety population) under placebo and 106 patients (94.6%) under Rowatinex were evaluable for efficacy.

There were 24 patients in the ITT population (seven patients under Placebo and 17 patients under Rowatinex) excluded from the PP. For details see Appendix 16.4, Listing 13.

The PP population therefore consists of 180 patients with 92 patients in the placebo group and 88 patients in the Rowatinex group.

Table 11-1: Analysis Populations

Population	Placebo	Rowatinex	Total
Enrolled patients	n.a.	n.a.	223
Safety Set (SAF)	110 (100)	112 (100)	222 (100)
ITT Population	98 (89.1)	106 (94.6)	204 (91.9)
ITT completer set (ITT-CS)	75 (68.2)	70 (62.5)	145 (65.3)
Per-protocol Population (PP)	92 (83.6)	88 (78.6)	180 (81.1)
PP completer set (PP-CS)	74 (67.3)	66 (58.9)	140 (63.1)

Remarks: The table gives the number and percent (in parentheses) of patients in each group from SAF.
Reference: Appendix 16.2, Table 1.2, Table 12.1.2: ITT-CS, Table 12.1.4: PP-CS

11.2 Demographic and Other Baseline Characteristics

Demographic and other baseline features displayed in this section are given for the safety population. For other populations see the corresponding tables in appendix 16.2.

In both treatment groups, there were slightly more men than women, and patients of the Rowatinex group were slightly older than those of the placebo group.

Table 11-2: Demographic characteristics (SAF)

	Statistics	Placebo N = 110	Rowatinex N = 112	Total N = 222
Gender				
Male	n (%)	59 (53.6)	66 (58.9)	125 (56.3)
Female	n (%)	51 (46.4)	46 (41.1)	97 (43.7)
Age	Mean ± SD	45.2 ± 15.2	50.4 ± 15.6	47.8 ± 15.6
	Median	47.0	51.0	49.0
	Range	18 – 78	18 – 82	18 – 82
	n	110	112	222

Remarks: n: number of patients, %: percent of patients, Mean: arithmetic mean, SD: standard deviation, Range: minimum - maximum
Reference: Appendix 16.2, Table 8.1

Vital signs at baseline are given in Table 11-3. In summary, no differences between the treatment groups could be found at baseline.

The same statement can be made for the other relevant populations (see Appendix 16.2, Tables 8.2 and 8.3).

Table 11-3: Vital signs at baseline (SAF)

	Statistics	Placebo N = 110	Rowatinex N = 112	Total N = 222
Weight [kg]	Mean ± SD	77.5 ± 14.4	76.5 ± 16.1	77.0 ± 15.3
	Median	77.5	76.0	77.0
	Range	45.0 – 113.0	43.0 – 120.0	43.0 – 120.0
Height [cm]	Mean ± SD	170.6 ± 8.6	169.2 ± 9.2	169.9 ± 8.9
	Median	170.0	170.0	170.0
	Range	150.0 – 186.0	138.0 – 186.0	138.0 – 186.0
BMI [kg/m²]	Mean ± SD	26.5 ± 4.3	26.6 ± 4.6	26.6 ± 4.4
	Median	26.4	26.5	26.4
	Range	18.7 – 40.0	18.0 – 39.8	18.0 – 40.0

Remarks: n: number of patients, %: percent of patients, Mean: arithmetic mean, SD: standard deviation, Range: minimum - maximum
Reference: Appendix 16.2, Table 8.1

For 15 patients in the placebo group (13.6%) and 16 patients in the Rowatinex group (14.3%) drug allergies were reported for the SAF population (see Appendix 16.2, Table 8.2).

Medical history and baseline conditions

Medical history data at baseline are summarized in Table 11-4 classified by system organ classes and sorted by their frequencies in the safety population.

Due to the initial disease the most frequent mentioned class was renal, urinary, and reproductive system disorders with equal relative frequencies in both treatment groups. Cardiovascular and gastrointestinal disorders occurred slightly more frequently in the Rowatinex than in the placebo group..

Table 11-4: Medical history by System Organ Classes (SAF)

SOC	Statistics	Placebo N = 110	Rowatinex N = 112	Total N = 222
Renal, urinary, and reproductive system disorders	n (%)	46 (41.8)	47 (42.0)	93 (41.9)
Cardiovascular disorders	n (%)	22 (20.0)	40 (35.7)	62 (27.9)
Gastrointestinal disorders	n (%)	16 (14.5)	28 (25.0)	44 (19.8)
Disorder of ear, nose, throat	n (%)	17 (15.5)	18 (16.1)	35 (15.8)
Musculoskeletal disorders	n (%)	11 (10.0)	10 (8.9)	21 (9.5)
Endocrine, metabolism disorders	n (%)	9 (8.2)	11 (9.8)	20 (9.0)
Disorder of head, neck	n (%)	2 (1.8)	4 (3.6)	6 (2.7)
Respiratory disorders	n (%)	2 (1.8)	4 (3.6)	6 (2.7)
Skin disorders	n (%)	3 (2.7)	1 (0.9)	4 (1.8)
Psychiatric disorders	n (%)	--	3 (2.7)	3 (1.4)
Neurological disorders	n (%)	--	3 (2.7)	3 (1.4)

Remarks: The table gives the number and percent (in parentheses) of patients in each group and in total. Not mentioned SOC's are not reported.
Reference: Appendix 16.2, Table 3.1

Previous stones

Occurrence of previous stones and their chemical composition, if known, are given in Table 11-5. No stones before current ESWL in the study were reported in 56% of patients in the Rowatinex group and 42% in the placebo group. This means it was a slightly higher proportion of patients under Rowatinex with first occurrence of kidney stones. The chemical composition was not known for most of the patients with previous stones. One patient of the placebo group had an apatite (calcium phosphat) kidney stone. There was one patient of each group with uric acid stones. Eleven of the placebo treated patients and ten of the Rowatinex patients had calcium-oxalate-dihydrate (weddellit) stones, the second common form of kidney stones. Altogether 18 patients (twelve from the placebo and six from the Rowatinex group) suffered from the most common whewellit stones (calcium-oxalate-monohydrate).

Table 11-5: Chemical composition of previous stone (SAF)

	Statistic	Placebo N = 110	Rowatinex N = 112	Total N = 222
No stone before	n (%)	46 (41.8)	63 (56.3)	109 (49.1)
Not known	n (%)	41 (37.3)	29 (25.9)	70 (31.5)
Apatite	n (%)	1 (0.9)	--	1 (0.5)
Whewellitt	n (%)	12 (10.9)	6 (5.4)	18 (8.1)
Weddellit	n (%)	11 (10.0)	10 (8.9)	21 (9.5)
Urinary acid	n (%)	1 (0.9)	1 (0.9)	2 (0.9)
Other	n (%)	1 (0.9)	1 (0.9)	2 (0.9)

Remarks: n (%): number and percent (in parentheses) of stones in each treatment group. Note: in patient 01-06 of the Rowatinex group, two stones are described. Only categories with entries are tabulated.
Reference: Appendix 16.2, Table 10.1

Characteristics of treated stone data and of treatment

The affected side of treated stones was slightly more frequently the right (55.9%) than the left (44.1%) kidney side.

Table 11-6: Characteristics of treated stone data (SAF)

	Statistic	Placebo N = 110		Rowatinex N = 112		Total N = 222	
Affected side		Left	Right	Left	Right	Left	Right
	n (%)	43 (39.1)	67 (60.9)	55 (49.1)	57 (50.9)	98 (44.1)	124 (55.9)
Position							
upper calix	n (%)	8 (7.3)	9 (8.2)	7 (6.3)	5 (4.5)	15 (6.8)	14 (6.3)
lower calix	n (%)	16 (14.5)	21 (19.1)	25 (22.3)	27 (24.1)	41 (18.5)	48 (21.6)
middle calix	n (%)	9 (8.2)	15 (13.6)	8 (7.1)	12 (10.7)	17 (7.7)	27 (12.2)
pyelum-PU passage	n (%)	5 (4.5)	13 (11.8)	10 (8.9)	9 (8.0)	15 (6.8)	22 (9.9)
Size	Mean ± SD	7.4 ± 3.7	8.6 ± 3.9	7.3 ± 3.1	8.1 ± 4.2	7.4 ± 3.4	8.3 ± 4.0
	Median	6.0	8.0	7.0	7.0	7.0	8.0
	Range	3 – 20	3 – 20	2 – 17	3 – 19	2 – 20	3 – 20
	n	43	68	54	57	97	125

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum, n: number of patients
n (%): number and percent (in parentheses) of stones in each treatment group. Note: in patient 01-06 of the Rowatinex group, two stones are described.
Reference: Appendix 16.2, Table 9.1

The distribution of the position was fairly similar in both treatment groups even if a slightly higher rate of occurrence in the lower calix was observed for the Rowatinex group. In summary the very most patients reported the treated stone in the lower calix (about 20%, see Table 11-6).

No difference of size of treated stone was observed between both treatment groups (Table 11-6).

The modal number of ESWL treatments was 3 in the placebo group but 6 in the Rowatinex group (Table 11-7). There were no essential differences between the groups observed in the real number of shock waves.

A slightly higher rate of patients under placebo than under Rowatinex was treated with ESWL under anaesthesy (Table 11-7).

Table 11-7: Number of treatments and intensity of waves (SAF)

	Statistic	**Placebo** N = 110	**Rowatinex** N = 112	**Total** N = 222
Number of ESWL treatments				
0	n (%)	--	1 (0.9)	1 (0.5)
1	n (%)	19 (17.3)	26 (23.2)	45 (20.3)
2	n (%)	16 (14.5)	13 (11.6)	29 (13.1)
3	n (%)	36 (32.7)	25 (22.3)	61 (27.5)
4	n (%)	12 (10.9)	14 (12.5)	26 (11.7)
5	n (%)	9 (8.2)	1 (0.9)	10 (4.5)
6	n (%)	18 (16.4)	32 (28.6)	50 (22.5)
Max. intensity of ESWL				
Missing	n (%)	--	1 (0.9)	1 (0.5)
1	n (%)	3 (2.7)	2 (1.8)	5 (2.3)
2	n (%)	13 (11.8)	15 (13.4)	28 (12.6)
3	n (%)	44 (40.0)	36 (32.1)	80 (36.0)
4	n (%)	22 (20.0)	24 (21.4)	46 (20.7)
5	n (%)	10 (9.1)	2 (1.8)	12 (5.4)
6	n (%)	18 (16.4)	32 (28.6)	50 (22.5)
ESWL under anaesthesy	n (%)	29 (26.4)	19 (17.0)	48 (21.6)

Remarks: n (%): number and percent (in parentheses) of stones in each treatment group
Note: in patient 01-06 of the Rowatinex group, two stones are described.
Reference: Appendix 16.2, Table 11.1

There were no significant differences between both treatment groups with respect to number of ESWL treatments (p=0.6185, Student's t-test) and the maximum intensity of ESWL (p=0.1979, Student's t-test; see Appendix 16.2, Tables 11.2 and 11.3).

11.3 Measurements of Treatment Compliance

Compliance of patients was evaluated by the number of used tablets (dispensed minus returned) related to the number of tablets that were planned to be used.

Treatment compliance is described in Table 11-8 for the ITT population. The average compliance rate on average was acceptable in both treatment groups (see medians). There was one patient under Rowatinex (06-180) who was only 5 days under medication but had received 200 tablets and returned none what resulted in a compliance of 666.7%. Another patient in the safety population (06-188) was only one day under medication and returned also no medication which resulted in 3,333.3% (see Appendix 16.4, Listing 12).

Table 11-8: Treatment compliance - Percent of visits (ITT)

		Placebo	**Rowatinex**	**Total**
	Statistic	N = 98	N = 106	N = 204
Treatment compliance	M ± SD	92.8 ± 15.1	98.2 ± 57.6	95.6 ± 42.8
	Median	96.6	95.3	95.7
	Range	24.4 – 142.9	24.7 – 666.7	24.4 – 666.7
	n	98	106	204
Treatment compliance				
< 80%	n (%)	9 (9.2)	15 (14.2)	24 (11.8)
> 120%	n (%)	1 (1.0)	4 (3.8)	5 (2.5)

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum
n (%): number and percent (in parentheses) of patients in each treatment group
Reference: Appendix 16.2, Table 5.2, 6.2

11.4 Efficacy Results

11.4.1 Analysis of efficacy

11.4.1.1 Analysis of primary efficacy criterion

11.4.1.1.1 *Definition of the analysis population*

According to the adaptive design of the study, results for primary efficacy are given for Part I (Interim Analysis - IA) and Part II (after IA) separately. After the overall end of the study the ITT and PP populations were specified and small corrections to the populations analyzed in the interim analysis became necessary. Six patients formerly designated to the SAF population were now available for the ITT analysis set, two of them were additionally included in the PP population (see Table 11-9). Five additional patients from the ITT population could be analyzed in the PP population in the final analysis.

Table 11-9: Patients changed the population against interim analysis

Center-Patient	Treatm.	Pop IA	Pop final	Reason
01-012	Placebo	SAF	SAF/ITT	last visit = V-2
03-198	Rowatinex	SAF	SAF/ITT	last visit = V-2
06-184	Rowatinex	SAF	SAF/ITT/PP	last visit = V-5, stone-free at V-2
01-007	Rowatinex	SAF	SAF/ITT	last visit = V-6
01-011	Rowatinex	SAF	SAF/ITT/PP	last visit = V-6
02-109	Rowatinex	SAF	SAF/ITT	last visit = V-6
01-033	Placebo	SAF/ITT	SAF/ITT/PP	stone-free at V-2
01-014	Placebo	SAF/ITT	SAF/ITT/PP	stone-free at V-3
04-068	Rowatinex	SAF/ITT	SAF/ITT/PP	stone-free at V-3
04-094	Placebo	SAF/ITT	SAF/ITT/PP	stone-free at V-3
02-121	Rowatinex	SAF/ITT	SAF/ITT/PP	stone-free at V-4

Remarks: Two-digit center number first, three-digit patient number second.

11.4.1.1.2 *Rate of patients with stone-free status within 12 weeks after ESWL*

Stone-free status is defined as first time when no stones were reported in the CRF.

In Table 11-10, an overview of stone-free patients per visit is given. The table shows that the rates of stone-free patients at all visits were higher for the Rowatinex group than in the placebo group, both for parts I + II separately and combined. At study end, the rate of stone-free patients was by 17.9% higher in the Rowatinex group (67.9%) than in the placebo group (50.0%).

Table 11-10: Patients with stone-free status per visit (ITT)

		Placebo			Rowatinex		
		Part I	Part II	I+II	Part I	Part II	I+II
	Statistics	**N = 59**	**N = 39**	**N = 98**	**N = 69**	**N = 37**	**N = 106**
V-2 (Week 1)	n (%)	11 (18.6)	3 (7.7)	14 (14.3)	16 (23.2)	6 (16.2)	22 (20.8)
V-3 (Week 4)	n (%)	17 (28.8)	12 (30.8)	29 (29.6)	32 (46.4)	15 (40.5)	47 (44.3)
V-4 (Week 8)	n (%)	27 (45.8)	15 (38.5)	42 (42.9)	39 (56.5)	20 (54.1)	59 (55.7)
V-5 (Week 12)	n (%)	30 (50.8)	19 (48.7)	49 (50.0)	43 (62.3)	29 (78.4)	72 (67.9)

Remarks: Number and percent of patients in each group and in total.
Reference: Appendix 16.2, Table 14.1

Table 11-11 summarizes the proportion of stone-free patients for the ITT population which is primary for the confirmatory efficacy evaluation, but includes also the other three populations for efficacy analysis.

Table 11-11: Number of stone-free patients until Week 12 (all efficacy populations)

	Part I		Part II		Part I + II	
	PLAC	ROWA	PLAC	ROWA	PLAC	ROWA
ITT	**N = 59**	**N = 69**	**N = 39**	**N = 37**	**N = 98**	**N = 106**
Stone-free patients.	30 (50.8)	43 (62.3)	19 (48.7)	29 (78.4)	49 (50.0)	72 (67.9)
1-sided p-value	0.1297		0.0069		0.0068	
Fisher's 1-sided p-value	n.a.		n.a.		**0.0009**	
2-sided p-value	0.1913		0.0074		0.0092	
Fisher's 2-sided p-value	n.a.		n.a.		0.0014	
ITT-CS	**N = 42**	**N = 42**	**N = 34**	**N = 28**	**N = 76**	**N = 70**
Stone-free patients.	21 (51.2)	29 (69.0)	17 (50.0)	23 (82.1)	38 (50.0)	52 (74.3)
1-sided p-value	0.0754		0.0082		0.0028	
Fisher's 1-sided p-value	n.a.		n.a.		<0.0001	
2-sided p-value	0.0971		0.0085		0.0034	
Fisher's 2-sided p-value	n.a.		n.a.		<0.0001	
PP	**N = 56**	**N = 53**	**N = 36**	**N = 35**	**N = 92**	**N = 88**
Stone-free patients.	30 (53.6)	40 (75.5)	18 (50.0)	29 (82.9)	48 (52.2)	69 (78.4)
1-sided p-value	0.0141		0.0034		0.0002	
Fisher's 1-sided p-value	n.a.		n.a.		<0.0001	
2-sided p-value	0.0171		0.0034		0.0002	
Fisher's 2-sided p-value	n.a.		n.a.		<0.0001	
PP-CS	**N = 41**	**N = 38**	**N = 33**	**N = 28**	**N = 74**	**N = 66**
Stone-free patients.	21 (51.2)	27 (71.1)	16 (48.5)	23 (82.1)	37 (50.0)	50 (75.8)
1-sided p-value	0.0574		0.0063		<0.0001	
Fisher's 1-sided p-value	n.a.		n.a.		0.0004	
2-sided p-value	0.0731		0.0064		0.0017	
Fisher's 2-sided p-value	n.a.		n.a.		0.0005	

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group
p-values are associated with the chi² test (2-sided) or with Fisher's exact test (1-sided)
Reference: Appendix 16.2, Table 12.1.1

For the primary efficacy variable, "stone-free at week 12", the 2-sided p-value of the first part of the study is p=0.1913 and of the second part, it is p=0.0074. If the two 1-sided p-values are multiplied, the product is p=0.0009. This p-value is below the Bauer-Köhne boundary of p=0.0038 and thus it is below the 1-sided significance level of $\alpha = 0.025$ which has been defined in the study protocol. With this result the study demonstrates superior efficacy of Rowatinex compared to placebo. The NNT (number needed to treat) is 5.6 which is clinically relevant.

The more favourable efficacy of Rowatinex compared to placebo in the primary endpoint as decribed for the ITT population is even more pronounced in the three other efficacy analysis populations. For the differences between both treatments in the PP, the 2-sided p-value in the

first part is p=0.0171, for the second part p=0.0034, and the pooled 1-sided p-value according to Fisher is p<0.0001. Here, the NNT = 3.8 which is highly clinically relevant. In general, all p-values of these additional exploratory analyses are below the critical p-value = 0.0038 according to Bauer & Köhne and thus strongly support the outcome of the primary efficacy analysis of stone-free patients.

11.4.1.1.3 *Rate of patients with "need for surgical interventions" within 12 weeks after ESWL*

In only two patients of the Rowatinex group, surgical interventions became necessary due to complications after the initial ESWL (p=0.2688, 1-sided Fisher's exact test). Both patients (02-142 and 06-253) suffered from fever, pyelonephritis and occlusion and a double-J clip was put in place.

In summary, no differences between both treatment groups could be observed with regard to a need for surgical interventions during the 12 weeks after the initial ESWL. These events were very rare in general.

11.4.1.2 Analysis of secondary efficacy criteria

11.4.1.2.1 *Time to stone-free status*

Summary results for life table analysis are given in Table 11-12. The median values for the placebo group are precarious because more than half of the patients were censored, which means that they were not stone-free at their individual study end. This was the reason to give in addition the mean values (and their standard errors), nevertheless they are also underestimated from the censored data.

Table 11-12: Life table analysis - time (days) to stone-free (ITT)

		Placebo	**Rowatinex**	
	Statistic	N = 98	N = 106	p-value
Part I	n	59	69	
	censored - n(%)	29 (49.2)	26 (37.7)	
	Mean ± SE	63.5 ± 4.5	58.6 ± 5.8	0.0477
	Median	91.0	35.0	
	95% CI	(56.0;.)	(29.0;67.0)	
Part II[(a)]	n	39	37	
	censored - n(%)	20 (51.3)	8 (21.6)	
	Mean ± SE	62.6 ± 4.7	63.0 ± 6.9	0.1383
	Median	85.0	62.0	
	95% CI	(59.0;.)	(30.0;86.0)	
Part I + II[(a)]	n	98	106	
	censored - n(%)	49 (50.0)	34 (32.1)	
	Mean ± SE	64.3 ± 3.4	59.8 ± 4.5	0.0061
	Median	85.0	56.0	
	95% CI	(59.0;.)	(30.0;84.0)	

Remarks: p-value (two-sided) is associated with log-rank test
Reference: Appendix 16.2, Table 17.1.1

The given p-values are one-sided versions of the log-rank tests in the life-table analysis. Due to the adaptive design with Fisher's test procedure the 1-sided p-values from single parts have to be multiplied (p(I)*p(II) = 0.0016) which is below the 1-sided Bauer-Köhne boundary of p=0.0038. The 2-sided p-value for the pooled analysis is p=0.0061.

Table 11-13: Life table analysis - time (days) to stone-free (Per-Protocol)

	Statistic	Placebo N = 92	Rowatinex N = 88	p-value
Part I	n	56	53	0.0220
	censored - n(%)	26 (46.4)	13 (24.5)	
	Mean ± SE	62.6 ± 4.6	53.8 ± 6.1	
	Median	84.0	31.0	
	95% CI	(56.0;.)	(28.0;63.0)	
Part II[(a)]	n	36	35	0.1134
	censored - n(%)	18 (50.0)	6 (17.1)	
	Mean ± SE	62.8 ± 4.9	62.4 ± 6.9	
	Median	85.0	62.0	
	95% CI	(59.0;.)	(29.0;86.0)	
Part I + II[(a)]	n	92	88	0.0028
	censored - n(%)	44 (47.8)	19 (21.6)	
	Mean ± SE	64.0 ± 3.5	57.1 ± 4.6	
	Median	85.0	49.5	
	95% CI	(59.0;.)	(29.0;64.0)	

Remarks: p-value is associated with log-rank test
Reference: Appendix 16.2, Table 17.1.3

For the PP population (Table 11-13), the 2-sided p-value for the first study period was p=0.0220 and for the second period, it was p=0.1134. The product of both 1-sided p-values according to Fisher calculated to (p(I)*p(II) = 0.0006 which also is below the 1-sided Bauer-Köhne boundary of p=0.0038. The 2-sided p-value for the pooled analysis is p=0.0028.

In the outcome variable "time to stone-free status", Rowatinex is markedly superior to placebo according to the median time to stone-free status of 56 days versus 85 days (ITT, see Table 11-12) or 49.5 days versus 85 days (PP, see Table 11-13).

Survival plots are provided in Table 17.1.1 (ITT) and in Table 17.1.3 (PP) in Appendix 16.2.

11.4.1.2.2 *Pain measured by a visual analogue scale (VAS)*

Course of pain during the study is given in Table 11-14. On average (mean), pain improved markedly but to a similar extent in both treatment groups. However, in statistical analysis (see Table 26), no differences between both groups could be detected.

Table 11-14: Pain (VAS) - Change from BL (ITT)

	Statistic	Placebo N = 98	Rowatinex N = 106
Baseline (day 1)	M ± SD	2.1 ± 2.3	2.1 ± 2.6
	Median	1.0	1.0
	Range	0.0 – 7.2	0.0 – 10.0
	n	98	106
change from BL LOCF (end of study)	M ± SD	-1.7 ± 2.6	-1.6 ± 2.5
	Median	-1.0	-0.4
	Range	-7.2 – 10.0	-10.0 – 3.4
	n	98	106

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum
Reference: Appendix 16.2, Table 26.1

11.4.1.2.3 *Responder and remitter in pain*

Responder and remitter in pain are defined as patients who reduced their pain from baseline of at least 50% (responder) or had no pain at all (score = 0) at the end of the study (remitter). Rates are shown in Table 11-15.

The great majority of all patients in both treatment groups showed clinically relevant improvements of pain which could be due to eg the natural course of the medical condition or the effectiveness of analgesics no differences between both treatment groups can be detected.

Table 11-15: Number of responder and remitter in pain (ITT)

	Statistic	Placebo N = 98	Rowatinex N = 106	p-value
Responder	n (%)	48 (81.4)	52 (81.3)	>0.999
Remitter	n (%)	71 (72.4)	74 (69.8)	0.76

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group
p-values associated with Fisher's exact test.
Reference: Appendix 16.2, Table 28.1

11.4.1.2.4 *Number of residual stones (ultrasound)*

The number of patients with residual stones as evaluated by ultrasound (positive findings in echodens area) as well as the number of residual stones is given in Table 11-16 for Day 1 and for the last available observation in the study (LOCF).

The rate of patients with residual stones at baseline was comparable in both treatment groups. The number of affected patients decreased in both groups. At the end of the study, tenden-

tially less patients with residual stones were observed in the Rowatinex group (27.4%) compared to the placebo group (39.8%) (Fisher's exact test: p=0.09945).

Table 11-16: Residual stones by ultrasound (ITT)

	Statistic	**Placebo** N = 98	**Rowatinex** N = 106
day 1			
missing	n (%)	1 (1.0)	--
existent echodens area	n (%)	81 (82.7)	87 (82.1)
number of stones	M ± SD	1.8 ± 1.3	2.1 ± 2.9
	Median	1.0	1.0
	Range	1 – 8	1 – 26
	N	81	86
Week 12			
missing	n (%)	12 (12.2)	27 (25.5)
existent echodens area	n (%)	35 (35.7)	17 (16.0)
number of stones	M ± SD	1.6 ± 1.0	1.3 ± 0.7
	Median	1.0	1.0
	Range	1 – 5	0 – 3
	N	34	17

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group
M: arithmetic mean, SD: standard deviation, Range: minimum – maximum
Reference: Appendix 16.2, Table 19.1

11.4.1.2.5 *Frequency distributions of different surgical interventions, ESWL complications, and clinical signs*

The number of patients affected by any treatment complications is very low, no detailed analysis will be presented here. The following tables and listings report the relevant data:

- Surgical interventions: Listing 5.2 in Appendix 16.4
- ESWL complications: Table 22.1 in Appendix 16.2.

Table 11-17 presents the rate of a few patients who reported clinical signs of ESWL complications. No differences in the frequency distributions were noted. Nausea was the most frequent clinical symptom.

Table 11-17: ESWL complications and clinical signs (ITT)

	Statistic	Placebo N = 98	Rowatinex N = 106
ESWL complication	n (%)	2 (2.0)	3 (2.8)
clinical sign	n (%)	8 (8.2)	10 (9.4)
Headache	n (%)	2 (2.0)	3 (2.8)
Vertigo	n (%)	1 (1.0)	2 (1.9)
Nausea	n (%)	4 (4.1)	5 (4.7)
Vomiting	n (%)	2 (2.0)	3 (2.8)
Eruption	n (%)	1 (1.0)	--
Other	n (%)	6 (6.1)	4 (3.8)

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group
Reference: Appendix 16.2, Table 22.1, 24.1

11.4.1.2.6 *Subgroup analyses*

Number of stone-free patients stratified by the size of the treated stone (≤ 8 mm or > 8 mm)

The numbers of stone-free patients per subgroup are presented in Tables 11-18. Obviously, Rowatinex was comparable effective in both layers. The general efficacy of Rowatinex was even more pronounced in the PP (Appendix 16.2, Table 66.2).

Table 11-18: Number of stone-free patients stratified by size of treated stone (ITT)

	Placebo N = 98	Rowatinex N = 106
Size ≤ 8 mm	35 (55.6)	56 (74.7)
Size > 8 mm	14 (40.0)	16 (53.3)

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group stratified by size. One patient (03-258) of the Rowatinex group was not included into Table 66.1 because of missing stone size. From Listing 5.1 and 5.2 size of stone could be identified and the patients was included in this Table 11-18 among those patients with stone size ≤ 8 mm.
Reference: Appendix 16.2, Table 66.1

Number of stone-free patients stratified by side and position of the treated stone

The numbers of stone-free patients stratified by side and position of the treated stone are presented in Table 11-19. Percentages in parentheses describe the proportion of stone-free patients within the given stratum. Rowatinex seems to be more effective in stones in the upper and lower left and right calyx.

Table 11-19: Number of stone-free patients stratified by side and position of treated stone (ITT)

	Placebo N = 98	Rowatinex N = 106
Right upper calyx	2 (28.6)	5 (100.0)
Right lower calyx	9 (50.0)	20 (76.9)
Right middle calyx	8 (57.1)	6 (54.5)
Right pyelum PU passage	5 (50.0)	5 (55.6)
Left upper calyx	1 (14.3)	6 (85.7)
Left lower calyx	5 (31.3)	17 (70.8)
Left middle calyx	5 (55.6)	2 (28.6)
Left pyelum PU passage	4 (100.0)	3 (37.5)

Remarks: n (%): number and percent (in parentheses) of patients in each treatment group stratified by position
Reference: Appendix 16.2, Table 64.1

11.4.2 Statistical / analytical issues

11.4.2.1 Adjustment for covariates

No adjustment for covariates was made for the primary analysis.

11.4.2.2 Handling of dropouts or missing data

For the patients of the ITT-population, missing values of the baseline measure of residual stones were not expected; otherwise these patients could not be randomized. For patients with missing values thereafter the LOCF-method (Last Observation Carried Forward) was used, i.e., the last observed value was taken as a substitute for the missing assessments. Patients with stone-free status at baseline were excluded from any efficacy analysis.

Missing values of the secondary parameters were only replaced for an endpoint analysis, applying the LOCF method.

11.4.2.3 Interim analyses and data monitoring

160 patients were planned to be randomized in six centers, at least 100 patients should be available for an interim analysis which became necessary due to administrative reasons (data to be delivered to the regulatory agency). The interim analysis was performed actually with 141 randomized patients and blinded treatment codes. Because of no definite advantage of

one treatment against the other (significance level for each primary efficacy criteria of 0.0102) and acceptable safety results the study was continued.

Data monitoring was performed under direction of HungaroTrial, Hungary. The procedures administered were described in a SOP.

11.4.2.4 Multicentre studies

Patients from six sites from Hungary contributed in the trial with a minimum of seven patients (1 center) and a maximum of 73 patients (1 center).

11.4.2.5 Multiple comparisons / multiplicity

To keep the overall level for error probability in hypothesis testing, at first an adaptive design was planned (see section 9.7.1.4). Secondly, the error probability of $\alpha = 0.05$ was partitioned in $\alpha = 0.025$ testing the two primary analysis variables simultaneously, time to stone-free status and surgical interventions due to complications. No further correction of the type I error was necessary.

The results of analyses with all secondary efficacy variables were interpreted in an exploratory manner.

11.4.2.6 Active-control studies intended to show equivalence

The study was intended to show superiority.

11.4.2.7 Examination of subgroups

Patients with initial residual stones of size ≤ 8 mm and > 8 mm were compared between the two treatment groups with respect to the primary efficacy variables in an exploratory manner. In addition, the rate of stone-free patients was analyzed according to position of stone prior to ESWL (upper, lower, middle calix, pyelum-PU passage for left and right side). These supportive analyses were performed both with the ITT and the PP population.

11.4.3 Tabulation of individual response data

For a comprehensive tabulation of individual response data see the Subject Data Listings (SDL) in Appendix 16.4.

11.4.4 Drug dose, drug concentration, and relationships to response

Not foreseen.

11.4.5 Drug-drug and drug-disease interactions

Not foreseen.

11.4.6 By-patient displays

Not foreseen.

11.5 Efficacy Conclusion

Rowatinex was superior to placebo with regard to a higher rate of stone-free patients after 12 weeks ($p<0.025$, 1-sided). The difference in the rate of stone-free patients of 17.9% is considered clinically relevant.

Treatment complications occurred in only 2 patients, no differences between both treatment groups could be demonstrated.

Also, time to stone-free status was shortened by approximately one month under Rowatinex compared to placebo ($p<0.025$, 1-sided).

Pain scores decreased under both treatment groups in a similar manner.

Rowatinex was comparably effective compared to placebo when the population was stratified by size of stone at the time of ESWL. Other subgroup analyses regarding position of stone showed that Rowatinex seemed to be more effective than placebo if the stone was positioned in the right and left upper and lower calyx.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Time under exposure was about 80 days for both treatment groups with comparable range and median (see Table 12-1). For one patient under Rowatinex no data was available.

Table 12-1: Time under exposure (SAF)

		Placebo	Rowatinex	Total
	Statistics	N = 110	N = 112	N = 222
Time under exposure (days)	Mean ± SD	81.6 ± 23.3	78.2 ± 27.7	79.9 ± 25.6
	Median	86.0	85.0	85.0
	Range	1 – 133	5 – 130	1 – 133
	n	110	111	221

Remarks: Mean: arithmetic mean, SD: standard deviation, Range: minimum - maximum
Reference: Appendix 16.2, Table 4.1

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

In the Rowatinex group 25 AEs were reported in 15 patients (13.4%) and in the placebo group 27 AEs were reported in 12 patients (10.9%). Seven AEs occurring in 4 patients (3.6%) were assessed as drug related in the Rowatinex group and two AEs in 2 patients (1.8%) of the placebo group. None of four SAEs (3 in 3 patients 2.7%) in the Rowatinex group and 1 in 1 patient (0.9%) in the placebo group) were considered drug-related by the investigators. Table 12-2 displays the number of patients who experienced at least one AE or SAE (see Appendix 16.2, Table 49: any AEs, Table 52: related AEs, Table 55: any SAEs, Table 58: related SAEs).

Table 12-2: Summary of patients with adverse events (SAF)

	Placebo N = 110		Rowatinex N = 112	
Relationship to study drug	**any**	**related**	**any**	**related**
AEs	12 (10.9)	2 (1.8)	15 (13.4)	4 (3.6)
Serious AEs	1 (0.9)	--	3 (2.7)	--

Remarks: The table gives number and percent (in parentheses) of patients with at least one AE, no multiple counts of episodes. Relationship to study drug: any: includes not related and related.
Reference: Appendix 16.2, Table 49: any AEs, Table 52: related AEs, Table 55: any SAEs, Table 58: related SAEs

A detailed description of SAEs is given in section 12.5.

12.3 Display of adverse events

Table 12-3 shows the number of patients with AEs stratified by severity. More than half of all AEs were mild, and only a small rate was of severe intensity. Only few patients were affected by drug related AEs and none of these AEs was assessed as severe. No remarkable differences were found between treatment groups, except for slightly more drug related AEs in the Rowatinex group.

Table 12-3: Patients with adverse events by intensity (SAF)

	Placebo N = 110		Rowatinex N = 112	
Relationship to study drug	**any**	**related[a)]**	**any**	**related[a)]**
Mild	8 (7.3)	2 (1.8)	9 (8.0)	2 (1.8)
Moderate	4 (3.6)	--	4 (3.6)	2 (1.8)
Severe	1 (0.9)	--	2 (1.8)	--

Remarks: The table gives number and percent (in parentheses) of events, no multiple counts of episodes. [a)]: The events are first classified in severity groups, whereas only the worst group is chosen, the relation to study drug is classified secondary with drug relationship being chosen before no drug relationship (see Appendix 16.4, Listing 9.2. Multiple counts for AEs occurring more than once in the same patient are included in the table.

Reference: Appendix 16.2, Table 50.2: any AEs, Table 53.2: related AEs

Table 12-4 summarizes AEs by system organ classes (MedDRA) and their relationship to study drug, sorted by frequencies in the total safety population. Most frequently recorded AEs were AEs of the system organ class gastrointestinal disorders and of the system organ class renal and urinary disorders.

Table 12-4: Patients with adverse events by system organ class and relationship to study drug (SAF)

	Placebo N = 110		Rowatinex N = 112	
Relationship to study drug	**any**	**related**	**any**	**related**
Gastrointestinal disorders	9 (8.2)	2 (1.8)	6 (5.4)	4 (3.6)
Renal and urinary disorders	5 (4.5)	--	3 (2.7)	--
Musculoskeletal and connective tissue	2 (1.8)	--	2 (1.8)	--
Infections and infestations	1 (0.9)	--	2 (1.8)	--
Nervous system disorders	1 (0.9)	--	2 (1.8)	1 (0.9)
Vascular disorders	1 (0.9)	--	1 (0.9)	--
Ear and labyrinth disorders	--	--	2 (1.8)	1 (0.9)
Cardiac disorders	--	--	1 (0.9)	--
Eye disorders	1 (0.9)	--	--	--
Reproductive system and breast disorders	1 (0.9)	--	--	--

Remarks: The table gives number and percent (in parentheses) of patients with at least one AE, no multiple counts of episodes. Organ class is presented in descending order of frequency in the total analysis set.

Reference: Appendix 16.2, Table 49: any, Table 52: related

In Table 12-5 the individual preferred terms are displayed for AEs which occurred in at least two patients in either treatment group.

Table 12-5: Patients with adverse events by system organ class, preferred term (≥ 2 patients in at least one treatment group), and relationship to study drug (SAF)

	Placebo N = 110		Rowatinex N = 112	
Relationship to study drug	**any**	**related**	**any**	**related**
Gastrointestinal disorders	9 (8.2)	2 (1.8)	6 (5.4)	4 (3.6)
Diarrhea	2 (1.8)	2 (1.8)	3 (2.7)	3 (2.7)
Nausea	6 (5.5)	--	4 (3.6)	1 (0.9)
Vomiting	4 (3.6)	--	3 (2.7)	1 (0.9)
Renal and urinary disorders	5 (4.5)	--	3 (2.7)	--
Nephrolithiasis	2 (1.8)	--	1 (0.9)	--
Renal colic	5 (4.5)	--	1 (0.9)	--
Musculoskeletal and connective tissue	2 (1.8)	--	2 (1.8)	--
Back pain	2 (1.8)	--	2 (1.8)	--
Nervous system disorders	1 (0.9)	--	2 (1.8)	1 (0.9)
Headache	1 (0.9)	--	2 (1.8)	1 (0.9)
Ear and labyrinth disorders	--	--	2 (1.8)	1 (0.9)
Vertigo	--	--	2 (1.8)	1 (0.9)

Remarks: The table gives number and percent (in parentheses) of patients with at least one AE, no multiple counts of episodes. Organ class is presented in descending order of frequency in the total analysis set.

Reference: Appendix 16.2, Table 49: any, Table 52: related

12.4 Analysis of adverse events

The number of reported AEs was rather small and of these again only a few AEs were assessed as drug related. The most frequently mentioned AEs belonged to "gastrointestinal disorders" and then to "renal and urinary disorders".

Nausea was the most frequently reported AE in both treatment groups but only one of such event in the Rowatinex group was supposed to be related to the study drug. Of note, all reported events of diarrhea were considered to be study drug related. Also of interest, renal colics occurred more frequencly in the control group (n=5) than in the Rowatinex group.

12.4.1 Listing of adverse events by patient

A by-patient listing of AEs is provided in Appendix 16.4, SDL 9.1 and 9.2.

12.5 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No patient died during the study.

There were four SAEs in four patients, three events in the Rowatinex group and one event in the placebo group. None of these SAEs were considered to be treatment-related by the investigators.

These events were deep vein thrombosis (SOC: vascular disorders), nephrolithiasis (renal and urinary disorders), and pyelonephritis (infections and infestations) in the Rowatinex group and a renal colic (renal and urinary disorders) in the placebo group. All events except pyelonephritis were assessed as severe. The SAE "renal colic" was reported as 'unlikely' related to the study treatment; all other SAEs were classified as 'not' related to the study drug. Patients with deep vein thrombosis and nephrolithiasis discontinued prematurely the study due to these events.

For more details see section 12.5.2.

Four patients discontinued prematurely due to AEs. All these patients belonged to the Rowatinex group. Two of these patients dropped out due to SAEs as already mentioned above.

Additionally, one patient discontinued prematurely due to diarrhea assessed as moderate but 'high probably' related to the study drug.

Another patient discontinued prematurely due to a mild and 'possibly' study drug related headache, nausea, and vertigo.

12.5.1 Listings of deaths, other serious adverse events, and other significant adverse events

Listings of all serious AEs are given in Appendix 16.4, SDL. 9.1 - 9.2 together with other AEs.

12.5.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

The following 'narratives' are based on reported entries in the CRFs.

Narratives of Serious Adverse Events

Rowatinex group

Center 1/ Patient No. 16/ Initial: KJ

Patient: 73 years old, female, Caucasian, BMI (baseline) 29.4
Population: ITT
Treatment: Rowatinex
Original term: Deep vein thrombosis in the left hind limb

The event started at 07 Mar 2004, 30 days after baseline and continued for 26 days until 01 Apr 2004. The event was assessed as severe and the patient discontinued the trial due to the SAE. The SAE was supposed to be not related to study medication and no additional therapy was reported.

Center 2/ Patient No. 142/ Initial: HS

Patient: 23 years old, female, Caucasian, BMI (baseline) 19.6
Population: ITT
Treatment: Rowatinex
Original term: Occlusion

It was reported that 'the treated stone accommodated in pyelourethral background and caused significant occlusion'. Start of the event was 26 Nov 2004, 21 days after baseline. A DJ-Clip was put in place which caused the symptoms (fever, pyelonephritis, nausea) to cease. The SAE was resolved the same day. The event was assessed as severe and the patient discontinued the trial due to it. The SAE was considered to be not related to study treatment.

Center 6/ Patient No. 253/ Initial: VK

Patient: 51 years old, female, Caucasian, BMI (baseline) 34.5
Population: PP
Treatment: Rowatinex
Original term: Occluded pyelonephritis on the right side

Start of the event was reported at 11 Jan 2006, three days after baseline and it was still ongoing at the end of the study. The subject was lost to follow-up with unknown date of last medication. Last reported visit was at Week 8 after baseline. The event was assessed as severe and required hospitalization. The SAE was supposed to be not related to study medication and no additional therapy was reported.

Placebo group

Center 1/ Patient No. 18/ Initial: GF

Patient: 61 years old, female, Caucasian, BMI (baseline) 39.1
Population: PP
Treatment: Placebo
Original term: Left side nephrotic colica

The event started at 21 Mar 2004, four days after baseline and was resolved the same day. The event was assessed as severe. Relationship to study medication was rated as '**unlikely**' and additional medication was reported.

12.5.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

The three SAEs which occurred during treatment with Rowatinex did not reveal a specific risk of Rowatinex. None of the SAEs was drug-related.

12.6 Clinical Laboratory Evaluation

12.6.1 Listing of individual laboratory measurements by patient and each abnormal laboratory value

Subject data listings (SDLs) of individual laboratory measurements by patient including each abnormal laboratory value are presented within Appendix 16.4, Listing 6.

12.6.2 Evaluation of each laboratory parameter

A short descriptive overview about abnormal laboratory values is given in Table 12-2 to Table 12-4. A more detailed analysis is given in Appendix 16.2, Tables 31-48.

Assessment of clinical significance of notable laboratory analytes was done by the investigators. These ratings were analysed by shift tables (Table 12-2 to Table 12-4). In general, such clinically significant abnormalities were seldom at any visit of the study. The majority of patients did not ever develop any significant abnormal laboratory values during the study.

Table 12-2: Significant abnormal laboratory values according to investigators - Hematology (SAF)

	Placebo[a]			Rowatinex[a]		
Hematology	Only at baseline	Only at Week12	At both visits	Only at baseline	Only at Week12	At both visits
		n = 87			n = 76	
RBC	4 (4.6)	3 (3.4)	11 (12.6)	2 (2.6)	7 (9.2)	2 (2.6)
		n = 87			n = 77	
WBC	8 (9.2)	2 (2.3)	4 (4.6)	5 (6.5)	5 (6.5)	2 (2.6)
		n = 87			n = 77	
Hemoglobin	2 (2.3)	1 (1.1)	8 (9.2)	1 (1.3)	6 (7.8)	2 (2.6)
		n = 86			n = 77	
Hematocrit	7 (8.1)	7 (8.1)	4 (4.7)	6 (7.8)	7 (9.1)	1 (1.3)
		n = 85			n = 75	
Platelets	4 (4.7)	--	--	1 (1.3)	1 (1.3)	--

Remarks: The table gives number and percent (in parentheses) of patients in each treatment group.
[a] Only patients with values on both visits are counted
Source: Appendix 16.2, Tables 31-35

Table 12-3: Significant abnormal laboratory values according to investigators - Serum Chemistry (SAF)

	Placebo[a]			Rowatinex[a]		
Serum Chemistry	Only at baseline	Only at Week12	At both visits	Only at baseline	Only at Week12	At both visits
		n = 71			n = 61	
Calcium	1 (1.4)	4 (5.6)	2 (2.8)	3 (4.9)	2 (3.3)	1 (1.6)
		n = 67			n = 56	
Phosphate	5 (7.5)	4 (6.0)	6 (9.0)	5 (8.9)	4 (7.1)	1 (1.8)
		n = 85			n = 76	
Blood glucose	11 (12.9)	7 (8.2)	12 (14.1)	8 (10.5)	10 (13.2)	10 (13.2)
		n = 77			n = 69	
Uric Acid	2 (2.6)	9 (11.7)	3 (3.9)	5 (7.2)	3 (4.3)	7 (10.1)
		n = 84			n = 71	
Bilirubin	1 (1.2)	2 (2.4)	4 (4.8)	6 (8.5)	6 (8.5)	--
		n = 88			n = 78	
Creatinine	7 (8.0)	5 (5.7)	1 (1.1)	10 (12.8)	2 (2.6)	3 (3.8)
		n = 65			n = 61	
ALP	2 (3.1)	1 (1.5)	1 (1.5)	1 (1.6)	1 (1.6)	--
		n = 81			n = 71	
SGOT	2 (2.5)	3 (3.7)	--	4 (5.6)	2 (2.8)	3 (4.2)
		n = 80			n = 71	
SGPT	4 (5.0)	7 (8.8)	2 (2.5)	6 (8.5)	3 (4.2)	5 (7.0)

Remarks: The table gives number and percent (in parentheses) of patients in each treatment group.
[a] Only patients with values on both visits are counted
Source: Appendix 16.2, Tables 36-44

Table 12-4: Clinical relevance of abnormal laboratory values according to investigators - Urine analysis (SAF)

	Placebo [a]			Rowatinex [a]		
Serum Chemistry	Only at baseline	Only at Week12	At both visits	Only at baseline	Only at Week12	At both visits
		n = 81			n = 73	
pH	--	--	--	--	--	--
		n = 82			n = 72	
WBC	13 (15.9)	7 (8.5)	5 (6.1)	8 (11.1)	5 (6.9)	6 (8.3)
		n = 83			n = 72	
RBC	19 (22.9)	7 (8.4)	5 (6.0)	16 (22.2)	2 (2.8)	8 (11.1)
		n = 29			n = 28	
Urine culture[b]	3 (10.3)	5 (17.2)	1 (3.4)	1 (3.6)	3 (10.7)	1 (3.6)

Remarks: The table gives number and percent (in parentheses) of patients in each treatment group.
[a] Only patients with values on both visits are counted
[b] Urine culture was assessed as positive/negative, number of positive patients is counted.
Source: Appendix 16.2, Tables 45-48

12.7 Vital Signs

Both for vital signs blood pressure and heart rate and for body temperature no main differences for the raw values could be found between the treatments groups at baseline and end of treatment (see Table 12-5 and Table 12-6). Additionally, changes in these vital signs between baseline and study end were comparable between both groups.

Table 12-5: Vital signs: change from baseline (LOCF) - descriptive analysis (SAF)

	Statistic	Placebo N = 110	Rowatinex N = 112
BP systolic [mmHg]			
Visit 1	M ± SD	130.0 ± 14.1	129.2 ± 14.7
	Median (Range)	130.0 (100.0 – 168.0)	130.0 (100.0 – 180.0)
Change from BL (LOCF)	M ± SD	-4.0 ± 12.4	-2.9 ± 11.6
	Median (Range)	0.0 (-40.0 – 40.0)	0.0 (-43.0 – 20.0)
BP diastolic [mmHg]			
Visit 1	M ± SD	81.5 ± 7.6	81.8 ± 10.6
	Median (Range)	80.0 (60.0 – 110.0)	80.0 (60.0 – 120.0)
Change from BL (LOCF)	M ± SD	-1.6 ± 7.6	-1.3 ± 10.2
	Median (Range)	0.0 (-30.0 – 14.0)	0.0 (-42.0 – 20.0)
Heart rate [bpm]			
Visit 1	M ± SD	73.3 ± 6.4	74.3 ± 8.1
	Median (Range)	72.0 (56.0 – 92.0)	72.0 (59.0 – 109.0)
Change from BL (LOCF)	M ± SD	-0.4 ± 6.7	-0.8 ± 8.3
	Median (Range)	0.0 (-24.0 – 15.0)	0.0 (-32.0 – 22.0)

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum
Reference: Appendix 16.2, Table 29

No clinically notable abnormalities in vital signs were observed during the study.

Table 12-6: Temperature: baseline and end of treatment (LOCF) - descriptive analysis (SAF)

	Statistic	Placebo N = 110	Rowatinex N = 112
Temperature [°C]			
Visit 1	M ± SD	36.6 ± 0.2	36.6 ± 0.2
	Median (Range)	36.6 (36.0 – 36.9)	36.6 (36.0 – 37.0)
	n	109	112
Visit 5 (week 12) (LOCF)	M ± SD	36.6 ± 0.2	36.6 ± 0.2
	Median (Range)	36.6 (36.0 – 37.0)	36.6 (36.0 – 36.9)
	n	110	112

Remarks: M: arithmetic mean, SD: standard deviation, Range: minimum – maximum
Reference: Appendix 16.2, Table 29

12.8 Safety Conclusion

A low rate of patients experienced adverse events during this study with similar frequency distribution of AEs in the Rowatinex and in the placebo group. AEs considered to be drug-related by the investigators were mainly gastrointestinal system disorders (diarrhea, nausea,

vomiting), headache and vertigo. None of the few serious adverse events were considered drug-related.

In summary, Rowatinex was tolerated well by the patients and safe.

13 DISCUSSION AND OVERALL CONCLUSION

Efficacy

The aim of this multi-centre, randomized, double-blind, therapeutic, parallel group trial was to demonstrate superiority of Rowatinex® as compared to placebo with respect to the rate of stone-free patients during 12 weeks of treatment after ESWL or the rate of patients requiring surgical intervention due to complications or stone residuals (two hierarchically ordered independent primary efficacy criteria).

Rowatinex was superior to placebo in the primary efficacy measure, rate of patients with stone-free status after 12.weeks of therapy. Every second placebo-treated patient was stone-free at Week 12 (50%), however more than two thirds (67.9%) were stone-free under Rowatinex. The difference in the rate of stone-free patients of 17.9% is statistically significant and considered also as clinically relevant.

Rowatinex was even more favourable than placebo in the per-protocol population and favourable efficacy of Rowatinex could also be supported by Kaplan-Meier analyses of time to stone free status. Stone-free status was achieved one month earlier under Rowatinex than under placebo.

Differences between Rowatinex and Placebo were similar in subgroups when the largest initial stone at the time of ESWL was stratified into smaller and larger stones (largest diameter of $\leq$ 8 mm vs. > 8 mm). However, more patients became stone-free when their kidney stone was below 8 mm. Rowatinex seems to be more effective in stones in the upper and lower left and right calyx compared to the middle calyx and the Pyelum passage.

In only two patients of the Rowatinex group, surgical interventions became necessary due to complications after the initial ESWL. Both patients suffered from fever, pyelonephritis and occlusion. There were no differences between the two groups in the second primary efficacy variable. Clinical signs during or after nephrolithiasis were infrequent; nausea was reported most frequently, however, with relative frequency of less than 5% in both groups.

No different changes in a pain VAS score could be shown. Patients of both groups improved markedly and slightly more than two thirds of the patients of both treatment groups were free of pain at study end.

Safety

During the course of the study there was only a small number of AEs as well as a few observations of abnormalities in laboratory parameters and vital signs. AEs related to Rowatinex

were diarrhea, nausea and vomiting as well as headache and vertigo. None of the few SAEs was drug-related according to the investigators.

Conclusions

Rowatinex is an efficacious treatment in eliminating calculi fragments generated by ESWL as compared to placebo. Treatment with Rowatinex is well tolerated and safe.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

End-of-text tables were not foreseen. For the post-text tables, please refer to Appendix 16.2, for the listings to Appendix 16.4.

14.1 Patients not treated

There was one patient enrolled but not randomized and therefore not treated. No further data of this patient were available.

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