Clinical trial results:
Detection of non-muscle invasive bladder cancer using PVP-Hypericin (Vidon®) fluorescence cystoscopy (Hypericin PDD)
A multi-centre, open, within-patient comparison, Phase IIb study

Summary

EudraCT number	2011-001819-30
Trial protocol	DE AT
Global end of trial date	19 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	Sano2011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sanochemia Pharmazeutika AG
Sponsor organisation address	Boltzmanngasse 11, Vienna, Austria, 1090
Public contact	Clinical Department, Sanochemia Pharmazeutika AG, Sano2011@sanochemia.at
Scientific contact	Clinical Department, Sanochemia Pharmazeutika AG, Sano2011@sanochemia.at

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2014
Global end of trial reached?	Yes
Global end of trial date	19 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To collect preliminary data on the diagnostic performance of Hypericin-guided cystoscopy regarding the detection of non-muscle invasive bladder cancer. Standard, white light cystoscopy will be compared with Hypericin assisted cystoscopy (PVP-Hypericin instillation; white light followed by blue light (Hypericin PDD) using a within-patient design by inspecting the bladder under white light first, followed by blue light.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP). Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 53
Country: Number of subjects enrolled	Germany: 169
Worldwide total number of subjects	222
EEA total number of subjects	222

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	145
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Adult male and female patients with a cystoscopically suspected bladder neoplasm scheduled for transurethral resection of the bladder (TURB) were screened at 10 investigational study sites (urology clinics) in 2 countries: Austria (2) and Germany (8) between 27 OCT 2011 (FPFV) and 19 JUL 2014 (LPLV).

Pre-assignment

Screening details:

Overall 227 patients were screened; 5 patients were screening failures (2 patients withrew their consent, 1 patient had unacceptable laboratory values, and 2 patients were not enrolled due to other reasons) and 222 patients were assigned to Hypericin PDD and TUR-B.

Period 1

Period 1 title	Overall trial / SEP (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Hypericin PDD

Arm description:

Within-patient design for comparison of standard, white light cystoscopy, with Hypericin-assisted cystoscopy (instillation of PVP-Hypericin, complete cystoscopic examination of the entire bladder under white light and then complete examination of the entire bladder surface under blue light; transurethral resection of the bladder).

Arm type	Within-patient comparison
Investigational medicinal product name	PVP-Hypericin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

IMP: 225 µg Sodium hypericin, 22.5 mg Polyvinylpyrrolidone and buffer (as lyophilized powder for reconstitution with water for injection).
Mode of Administration: Intravesical instillation via a urinary catheter.
Single intravesical instillation of 30 (+ 5) minutes duration followed by emptying of the bladder.

Number of subjects in period 1	Hypericin PDD
Started	222
Completed	222

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial / SEP

Reporting group description:

Safety Evaluable Population (SEP): the safety population included all treated patients with post-treatment efficacy data. The SEP was analysed mainly with respect to drug safety.
Of 222 patients assigned to photodynamic diagnosis (PDD) using Hypericin and TUR-B, 50 patients were used to standardise the study procedures (training patients), and 172 patients were regular patients. 2 patients terminated the study prematurely after Visit 2. TUR-B was not done in both patients either because of the appearance of a nontolerable AE which was not related to the study medication or due to problems with the blue light of the PDD System.
Among the 172 regular patients, 20 patients were included in the subgroup with PK sampling.
All 222 patients (50 training patients and 172 regular patients) received a single intravesical instillation of 50 mL reconstituted solution containing 225 µg Hypericin for PDD of bladder cancer at Visit 2 (day of surgery).

Reporting group values	Overall trial / SEP	Total	
Number of subjects	222	222	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	61	61	
From 65-84 years	145	145	
85 years and over	16	16	
Age continuous Units: years			
median	69.6		
standard deviation	± 10.6	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	179	179	
Ethnic origin Units: Subjects			
White	222	222	
Initial and/or recurrent bladder cancer			
Patients with initial and/or recurrent bladder cancer were scheduled for TUR-B of a suspected bladder cancer based on recent cystoscopic findings.			
Units: Subjects			
multiple tumours / suspicious lesions present	221	221	
one suspicious lesion only	1	1	
Pre-study cystoscopy Units: Subjects			

Pre-study cystoscopy done at study site	220	220	
Not done at study site	2	2	
Baseline 12-lead ECG done at study site			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP. The baseline ECG (Visit 1) was missing for 13/222 patients most commonly due to an error by the study site (10 patients), or because a pre-study ECG was available (2 patients), or due to logistic reasons (1 Patient) (SEP).			
Units: Subjects			
ECG done	209	209	
ECG missing	13	13	
Findings in 12-lead ECG			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP. Of the 209 patients who had a 12-lead ECG recorded at baseline, 41 patients had abnormal findings.			
Units: Subjects			
Abnormal findings	41	41	
No findings	168	168	
ECG Missing	13	13	
Physical examination performed Units: Subjects			
Yes	221	221	
No	1	1	
Vital signs measured Units: Subjects			
Yes	221	221	
No	1	1	
Findings Interfering with PVP-Hypericin Units: Subjects			
No	221	221	
Yes	0	0	
Missing	1	1	
Urine culture / urine pH Units: Subjects			
Normal	212	212	
Abnormal	10	10	
Urinalysis Erythrocytes			
Baseline urinalysis			
Units: Subjects			
Pos	126	126	
Neg	94	94	
Nd	0	0	
Missing	2	2	
Urinalysis Leucocytes			
Baseline urinalysis			
Units: Subjects			
Pos	47	47	
Neg	173	173	
Nd	2	2	
Missing	0	0	
Urinalysis Nitrite			
Baseline Urinalysis			
Units: Subjects			
Pos	4	4	

Neg	216	216	
Nd	2	2	
Missing	0	0	
Urinalysis Urine culture			
Baseline Urinalysis			
Units: Subjects			
Pos	20	20	
Neg	192	192	
Nd	10	10	
Missing	0	0	
Height			
Units: cm			
arithmetic mean	173.1		
standard deviation	± 7.64	-	
Weight			
Units: kg			
arithmetic mean	80.9		
standard deviation	± 15.02	-	

Subject analysis sets

Subject analysis set title	Diagnostic Performance / Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS)
The FAS for the efficacy analyses included all treated patients with available data to evaluate the primary endpoint. This meant, that both treatments (white light and blue light) had to be applied and the respective efficacy data were required in order to calculate the primary endpoint. This analysis set was used for the confirmatory test of the primary endpoint.
Of 222 patients assigned to photodynamic diagnosis (PDD) using Hypericin and TUR-B, 50 patients were used to standardise the study procedures (training patients), and 172 patients were regular patients. Of 172 regular patients who had Hypericin PDD, 2 patients terminated the study prematurely after Visit 2.

Subject analysis set title	Efficacy Ta lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup Ta: Diagnostic performance regarding papillary tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for Ta lesions separately on a per patient level.

Subject analysis set title	Efficacy T1 lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup T1: Diagnostic performance regarding papillary tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for T1 lesions separately on a per patient level.

Subject analysis set title	Efficacy Tis lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup Tis: Diagnostic performance regarding flat tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for Tis lesions separately on a per patient level.

Subject analysis set title	False-positive Rate
Subject analysis set type	Full analysis

Subject analysis set description:

Detection rates of benign lesions as false positive rates on a per patient level.
False positive rate was derived as the number of false positive lesions detected with white or blue light

divided by the total number of lesions suspected with white light or blue light, respectively.

Subject analysis set title	Pharmacokinetic (PK)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK subgroup (20 patients) included all FAS patients with PK sampling who had a second postoperative control examination (Visit 4) and valid data for the evaluation of Hypericin pharmacokinetics.

Reporting group values	Diagnostic Performance / Full Analysis Set (FAS)	Efficacy Ta lesions	Efficacy T1 lesions
Number of subjects	170	124	45
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	47		
From 65-84 years	111		
85 years and over	12		
Age continuous			
Units: years			
median	69.3		
standard deviation	± 10.85	±	±
Gender categorical			
Units: Subjects			
Female	33		
Male	137		
Ethnic origin			
Units: Subjects			
White	170		
Initial and/or recurrent bladder cancer			
Patients with initial and/or recurrent bladder cancer were scheduled for TUR-B of a suspected bladder cancer based on recent cystoscopic findings.			
Units: Subjects			
multiple tumours / suspicious lesions present	169		
one suspicious lesion only	1		
Pre-study cystoscopy			
Units: Subjects			
Pre-study cystoscopy done at study site	168		
Not done at study site	2		
Baseline 12-lead ECG done at study site			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP. The baseline ECG (Visit 1) was missing for 13/222 patients most commonly due to an error by the study site (10 patients), or because a pre-study ECG was available (2 patients), or due to logistic reasons (1 Patient) (SEP).			
Units: Subjects			

ECG done	165		
ECG missing	5		
Findings in 12-lead ECG			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP. Of the 209 patients who had a 12-lead ECG recorded at baseline, 41 patients had abnormal findings.			
Units: Subjects			
Abnormal findings	35		
No findings	130		
ECG Missing	5		
Physical examination performed Units: Subjects			
Yes	170		
No	170		
Vital signs measured Units: Subjects			
Yes	169		
No	1		
Findings Interfering with PVP-Hypericin Units: Subjects			
No	170		
Yes	0		
Missing	0		
Urine culture / urine pH Units: Subjects			
Normal	162		
Abnormal	8		
Urinalysis Erythrocytes			
Baseline urinalysis			
Units: Subjects			
Pos	96		
Neg	72		
Nd	0		
Missing	2		
Urinalysis Leucocytes			
Baseline urinalysis			
Units: Subjects			
Pos	33		
Neg	135		
Nd	2		
Missing	0		
Urinalysis Nitrite			
Baseline Urinalysis			
Units: Subjects			
Pos	2		
Neg	166		
Nd	2		
Missing	0		
Urinalysis Urine culture			
Baseline Urinalysis			
Units: Subjects			
Pos	15		

Neg	146		
Nd	9		
Missing	0		
Height			
Units: cm			
arithmetic mean	173.0		
standard deviation	± 7.79	±	±
Weight			
Units: kg			
arithmetic mean	81.6		
standard deviation	± 15.38	±	±

Reporting group values	Efficacy Tis lesions	False-positive Rate	Pharmacokinetic (PK)
Number of subjects	20	103	20
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnic origin			
Units: Subjects			
White			
Initial and/or recurrent bladder cancer			
Patients with initial and/or recurrent bladder cancer were scheduled for TUR-B of a suspected bladder cancer based on recent cystoscopic findings.			
Units: Subjects			
multiple tumours / suspicious lesions present			
one suspicious lesion only			
Pre-study cystoscopy			
Units: Subjects			
Pre-study cystoscopy done at study site			
Not done at study site			
Baseline 12-lead ECG done at study site			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP.			

The baseline ECG (Visit 1) was missing for 13/222 patients most commonly due to an error by the study site (10 patients), or because a pre-study ECG was available (2 patients), or due to logistic reasons (1 Patient) (SEP).			
Units: Subjects			
ECG done ECG missing			
Findings in 12-lead ECG			
A baseline 12-lead ECG was done in 209/222 patients included in the SEP. Of the 209 patients who had a 12-lead ECG recorded at baseline, 41 patients had abnormal findings.			
Units: Subjects			
Abnormal findings No findings ECG Missing			
Physical examination performed Units: Subjects			
Yes No			
Vital signs measured Units: Subjects			
Yes No			
Findings Interfering with PVP-Hypericin Units: Subjects			
No Yes Missing			
Urine culture / urine pH Units: Subjects			
Normal Abnormal			
Urinalysis Erythrocytes			
Baseline urinalysis			
Units: Subjects			
Pos Neg Nd Missing			
Urinalysis Leucocytes			
Baseline urinalysis			
Units: Subjects			
Pos Neg Nd Missing			
Urinalysis Nitrite			
Baseline Urinalysis			
Units: Subjects			
Pos Neg Nd Missing			
Urinalysis Urine culture			

Baseline Urinalysis			
Units: Subjects			
Pos			
Neg			
Nd			
Missing			
Height			
Units: cm			
arithmetic mean			
standard deviation	±	±	±
Weight			
Units: kg			
arithmetic mean			
standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Hypericin PDD

Reporting group description:

Within-patient design for comparison of standard, white light cystoscopy, with Hypericin-assisted cystoscopy (instillation of PVP-Hypericin, complete cystoscopic examination of the entire bladder under white light and then complete examination of the entire bladder surface under blue light; transurethral resection of the bladder).

Subject analysis set title	Diagnostic Performance / Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS)
The FAS for the efficacy analyses included all treated patients with available data to evaluate the primary endpoint. This meant, that both treatments (white light and blue light) had to be applied and the respective efficacy data were required in order to calculate the primary endpoint. This analysis set was used for the confirmatory test of the primary endpoint.
Of 222 patients assigned to photodynamic diagnosis (PDD) using Hypericin and TUR-B, 50 patients were used to standardise the study procedures (training patients), and 172 patients were regular patients. Of 172 regular patients who had Hypericin PDD, 2 patients terminated the study prematurely after Visit 2.

Subject analysis set title	Efficacy Ta lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup Ta: Diagnostic performance regarding papillary tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for Ta lesions separately on a per patient level.

Subject analysis set title	Efficacy T1 lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup T1: Diagnostic performance regarding papillary tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for T1 lesions separately on a per patient level.

Subject analysis set title	Efficacy Tis lesions
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Full Analysis Set (FAS) / subgroup Tis: Diagnostic performance regarding flat tumours per patient; detection rate of Hypericin PDD versus standard (white light) cystoscopy for Tis lesions separately on a per patient level.

Subject analysis set title	False-positive Rate
Subject analysis set type	Full analysis

Subject analysis set description:

Detection rates of benign lesions as false positive rates on a per patient level.
False positive rate was derived as the number of false positive lesions detected with white or blue light divided by the total number of lesions suspected with white light or blue light, respectively.

Subject analysis set title	Pharmacokinetic (PK)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK subgroup (20 patients) included all FAS patients with PK sampling who had a second postoperative control examination (Visit 4) and valid data for the evaluation of Hypericin pharmacokinetics.

Primary: Diagnostic performance of Hypericin-assisted cystoscopy / Sensitivity per patient

End point title	Diagnostic performance of Hypericin-assisted cystoscopy / Sensitivity per patient[1]

End point description:

The primary endpoint variable was the percentage of patients in whom non-muscle invasive bladder cancer (Tis and/or Ta/T1) is detected by Hypericin-assisted cystoscopy (PVP-Hypericin instillation;white light followed by blue light) as confirmed by biopsy results. The primary endpoint was defined as the percentage of patients in whom additional non-muscle invasive bladder cancer (Tis and/or Ta/T1) could be detected by Hypericin-assisted cystoscopy compared to standard white light cystoscopy, as confirmed by biopsy results.

End point type	Primary

End point timeframe:

Visit 2 (day of surgery) and biopsy result (after visit 3/4).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The database does not allow for statistical analysis for studies with a single arm within-patient comparison.
A confirmatory analysis was done for the primary endpoint. A confirmatory analysis (one-sided Mc-Nemar Test) was done in the FAS for the primary endpoint. All further statistical analyses were explorative.

End point values	Diagnostic Performance / Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	170			
Units: Improved sensitivity / Difference in %				
number (confidence interval 95%)	17.8 (9.8 to 25.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Diagnostic performance regarding flat and papillary tumours per patient

End point title	Diagnostic performance regarding flat and papillary tumours per patient

End point description:

Detection rate of Hypericin PDD versus standard (white light) cystoscopy for Tis, Ta and T1 lesions separately on a per patient level.

End point type	Secondary

End point timeframe:

Visit 2 (day of surgery) and biopsy result (after Visit 3/4)

End point values	Efficacy Ta lesions	Efficacy T1 lesions	Efficacy Tis lesions	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	124	45	20	
Units: Improved sensitivity / Difference in %				
number (confidence interval 95%)	14.5 (6.9 to 21.7)	13.3 (0.8 to 24.7)	35.0 (4.0 to 59.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: False Positive Rate per patient

End point title	False Positive Rate per patient

End point description:

The false positive rate was derived as the number of false positive lesions detected with white or blue light divided by the total number of lesions suspected with white light or blue light, respectively.
The false positive rate was calculated for standard white light and Hypericin PDD using the McNemar test for paired proportions.

End point type	Secondary

End point timeframe:

Visit 2 (day of surgery) and biopsy result (after Visit 3/4)

End point values	False-positive Rate			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: Difference in false positive rates in %				
number (confidence interval 95%)	14.6 (-0.2 to 28.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic

End point title	Pharmacokinetic

End point description:

Systemic absorption and pharmacokinetics of Hypericin after a single intravesical instillation of PVP-Hypericin (sub-group analysis).

End point type	Secondary

End point timeframe:

Blood sampling for pharmacokinetics was done frequently, 24 hour-profile, from
Visit 2 (before surgery) to Visit 3 (1st post-operative day), and once on Visit 4 (7th - 8th postoperative day) to obtain a complete pharmacokinetic profile.

End point values	Pharmacokinetic (PK)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: ng/mL				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded in detail (starting with insertion of the urinary catheter for instillation of PVP-Hypericin), at each post-baseline assessment (Visits 2 - 3 and Visits 2 - 4 for the sub-group with PK sampling, respectively).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	Safety evaluable population (SEP)

Reporting group description: -

Serious adverse events	Safety evaluable population (SEP)		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 222 (9.01%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Bladder perforation			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	14 / 222 (6.31%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Urinary retention postoperative			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 222 (0.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal pain			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety evaluable population (SEP)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 222 (51.80%)		
Investigations			
Blood glucose fluctuation			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Body temperature increased			

subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Application site pain			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		
Catheter site pain			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Device occlusion			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Post procedural constipation			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		
Post procedural haemorrhage			
subjects affected / exposed	68 / 222 (30.63%)		
occurrences (all)	68		
Postoperative fever			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	16 / 222 (7.21%)		
occurrences (all)	16		
Puncture site pain			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Urinary retention postoperative			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Vascular disorders			

Hypertension			
subjects affected / exposed	5 / 222 (2.25%)		
occurrences (all)	5		
General disorders and administration site conditions			
Application site irritation			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 222 (0.45%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 222 (1.80%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 222 (0.90%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 1 / 222 (0.45%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 2 / 222 (0.90%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 222 (0.45%) 1		
Renal and urinary disorders Bladder spasm subjects affected / exposed occurrences (all) Dysuria subjects affected / exposed occurrences (all) Hydronephrosis subjects affected / exposed occurrences (all) Urinary bladder haemorrhage subjects affected / exposed occurrences (all)	 22 / 222 (9.91%) 22 1 / 222 (0.45%) 1 1 / 222 (0.45%) 1 1 / 222 (0.45%) 1		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 222 (1.35%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2012	The amendment was requested by Sanochemia Pharmazeutika AG after first practical experience with the protocol. Adaptations of the respective inclusion diagnosis and inclusion criteria were made. In addition, the section about sample size was changed in order to allow an increased enrolment of further training patients, if deemed necessary. Furthermore, some administrative changes were included. These changes have substantial implications on the population of patients and the conduct of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported