Clinical trial results:
Prospective, randomised, controlled, multi-centre Phase III study for rapid identification of low risk patients after surgical partial liver resection through application of the LiMAx test

Summary

EudraCT number	2010-023095-31
Trial protocol	DE
Global end of trial date	01 September 2015

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017
Summary attachment (see zip file)	Study_Report_Synopsis (160318_Study_Report_Hum 001_v01-00_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	HUM-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01785082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Humedics GmbH
Sponsor organisation address	Marie-Elisabeth-Lüdersstr. 1, Berlin, Germany, 10625
Public contact	Clinical Trials Information, Humedics GmbH, +49 30 590083 240, alexander.helmke@humedics.de
Scientific contact	Clinical Trials Information, Humedics GmbH, +49 30 590083 240, alexander.helmke@humedics.de

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	17 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2015
Global end of trial reached?	Yes
Global end of trial date	01 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate efficacy, safety and benefit/risk analysis of a intravenously administered 13C-methacetin solution as a diagnostic agent for the measurement of liver function according to the LiMAx procedure compared to a control group representing the clinical standard of care in patients undergoing partial liver resection.
To show the impact on diagnostic thinking and therapeutic decision making based on a modified postoperative management (fast-track procedure) with direct transfer of patients with sufficient liver status from the recovery room to the general ward. By evaluating the clinical outcome and safety of the diagnostic approach of the LiMAx test, a benefit for the patient due to improved patient management compared to the standard of care procedure should be demonstrated.
As decisive target parameter for the decision on postoperative management under fast-track procedure, a postoperative LiMAx value of >150 µg/kg/h was to be established.

Protection of trial subjects:

Performance of a LiMAx test with the CE-certified measurement device of the company Humedics GmbH under use of the CE certified disposable accessories (breathing mask set) provided by the company.
Selection of study sites with capacity for potential double room occupancy planning (general ward and INT) for transfer from the recovery room for patients of the LiMAx group: In the event of unforeseeable events in the LiMAx group, if a transfer according to the result of the LiMAx test is not medically justifiable, beds are reserved for transfer.
Evaluation of the extra-hepatic reasons that stand contrary to a primary transfer to general ward: The specific exception (non-transfer to general ward due to extra-hepatic reasons) from the primary decision for transfer to general ward is in both test positive cases (LiMAx value > 150 µg/kg/h, respectively transfer according to OP plan to general ward in the control group) evaluated in the recovery room.
Criteria assessed by the responsible physician in the recovery room:
1. Relevant subsequent bleeding
2. No spontaneous respiration or no sufficient oxygenation under a maximum of 2 l/min oxygen with spontaneous respiration
3. Not sufficiently awake and responsive
4. Not treatable delirium
5. Haemodynamically unstable
6. No satisfactory level of analgesia
   Or due to a different medical decision with justification

Background therapy: -

Evidence for comparator:

usual clinical standard transfer practice

Actual start date of recruitment	23 January 2013
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	Germany: 149

Worldwide total number of subjects	149
EEA total number of subjects	149

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)	94
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

6 sites in Germany

Pre-assignment

Screening details:

149 patients were assessed for eligibility; of which 1 patient was a screening failure (violation of one inclusion criterion) excluded and not randomised. An additional 25 randomised patients were excluded and replaced in accordance with the study protocol.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As the randomisation took place after completion of the surgery planning, the surgeon was blinded with regard to the assignment of the patient to the LiMAx or the control group.
The correctness of the primary transfer to INT was retrospectively assessed in both groups. The post-operatively recorded patient data of all patients who were primarily transferred to INT are assessed in a blinded procedure by an independent committee.

Arms

Are arms mutually exclusive?	Yes
Arm title	LiMAx group

Arm description:

Perioperative management of the patients according to the fast-track procedure (Novum) comprising pre- and postoperative measurement of the liver function by means of the LiMAx test. Therefore, the investigational medicinal product was administered twice. The postoperative LiMAx test was performed in the recovery room.

Arm type	Experimental
Investigational medicinal product name	13C-Methacetin Solution for Injection (formerly named 13C-Methacetin Solution for Infusion)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.4% 13C-Methacetin Solution
Dosage: 2 mg/kg body weight-adjusted

Arm title	Control group

Arm description:

Perioperative management of the patients according to the clinical standard of care (standard transfer practice based on defined treatment and diagnostic algorithms)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	LiMAx group	Control group
Started	76	72
Surgery according to protocol	58	57
Completed	58	57
Not completed	18	15
Complications during operation	1	-
Surgery not performed according to protocol	13	12
LiMAx test postoperative not feasible	3	-
Protocol deviation	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 149 patients were assessed for eligibility; of which 1 patient was a screening failure (violation of one inclusion criterion) excluded and not randomised.

Baseline characteristics

Reporting groups	
Reporting group title	LiMAx group
Reporting group description:	
Perioperative management of the patients according to the fast-track procedure (Novum) comprising pre- and postoperative measurement of the liver function by means of the LiMAx test. Therefore, the investigational medicinal product was administered twice. The postoperative LiMAx test was performed in the recovery room.	
Reporting group title	Control group
Reporting group description:	
Perioperative management of the patients according to the clinical standard of care (standard transfer practice based on defined treatment and diagnostic algorithms)	

Reporting group values	LiMAx group	Control group	Total
Number of subjects	76	72	148
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	51	94
From 65-84 years	33	21	54
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.5	56.2	
standard deviation	± 13.2	± 14.6	-
Gender categorical Units: Subjects			
Female	32	33	65
Male	44	39	83
Race Units: Subjects			
Caucasian	76	72	148
Reasons for surgery			
Baseline disease characteristics			
Units: Subjects			
HCC (hepatocellular carcinoma)	13	8	21
CCC (cholangiocelluar carcinoma)	9	5	14
Liver metastases - colorectal	27	34	61
Liver metastases - melanoma	3	1	4
Adenoma (liver)	4	4	8
Focal nodular hyperplasia	2	3	5
Other	7	12	19
Other liver metastases	11	5	16

Relevant concomitant diseases			
Baseline disease characteristics			
Units: Subjects			
Chronic hepatitis B	1	1	2
Chronic hepatitis C	0	0	0
Non-alcoholic steatohepatitis (NASH)	3	1	4
Autoimmune hepatitis	0	0	0
Primary biliary cirrhosis (PBC)	0	0	0
Primary sclerotic cholangitis (PSC)	0	0	0
Liver cirrhosis	0	0	0
Hepatic steatosis	14	10	24
None	58	60	118
Previous surgery or therapy			
Baseline disease characteristics			
Units: Subjects			
Yes	70	69	139
No	6	3	9
Intake of medication 30 days before inclusion			
Baseline disease characteristics			
Units: Subjects			
Yes	57	55	112
No	19	17	36
Weight			
Units: kg			
arithmetic mean	78.7	80.1	
standard deviation	± 16.6	± 16.8	-
Height			
Units: cm			
arithmetic mean	170.6	171.8	
standard deviation	± 8.6	± 9.0	-

Subject analysis sets

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized patients (n=148, LiMAx group: n=76, control group: n=72).

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The following patients were included in the modified Intention-to-treat population:
1. Randomised patients (control group).
2. Randomised patients with a postoperative LiMAx test (LiMAx group).
3. None of the following exceptions occurred:
 a. The planned liver resection was not done or was postponed for more than 72 hours.
 b. The required OPS code (5-502) was changed during surgery and/or surgery discontinued due to extended tumour progression.
 c. Death of patient during surgery.
 d. The planned liver resection had to be extended by an unplanned surgery concerning other solid organs.
 e. Leukocyte count was less than 1/nl before surgery (visit 4a).
 f. Elevated measures of ALT or AST, higher than 1000 units/l before surgery .

Reporting group values	Safety	mITT	
Number of subjects	148	118	
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)	94	77	
From 65-84 years	54	41	
85 years and over	0		
Age continuous Units: years			
arithmetic mean	57.9	56.9	
standard deviation	± 13.9	± 14.2	
Gender categorical Units: Subjects			
Female	65	53	
Male	83	65	
Race Units: Subjects			
Caucasian	148	118	
Reasons for surgery			
Baseline disease characteristics			
Units: Subjects			
HCC (hepatocellular carcinoma)	21	18	
CCC (cholangiocelluar carcinoma)	14	10	
Liver metastases - colorectal	61	44	
Liver metastases - melanoma	4	4	
Adenoma (liver)	8	8	
Focal nodular hyperplasia	5	4	
Other	19	18	
Other liver metastases	16	12	
Relevant concomitant diseases			
Baseline disease characteristics			
Units: Subjects			
Chronic hepatitis B	2	2	
Chronic hepatitis C	0	0	
Non-alcoholic steatohepatitis (NASH)	4	4	
Autoimmune hepatitis	0	0	
Primary biliary cirrhosis (PBC)	0	0	
Primary sclerotic cholangitis (PSC)	0	0	
Liver cirrhosis	0	0	
Hepatic steatosis	24	17	

None	118	97	
Previous surgery or therapy			
Baseline disease characteristics			
Units: Subjects			
Yes	139	110	
No	9	8	
Intake of medication 30 days before inclusion			
Baseline disease characteristics			
Units: Subjects			
Yes	112	91	
No	36	27	
Weight			
Units: kg			
arithmetic mean	79.4	80.12	
standard deviation	± 16.6	± 15.58	
Height			
Units: cm			
arithmetic mean	171.2	171.56	
standard deviation	± 8.8	± 8.63	

End points

End points reporting groups

Reporting group title	LiMAx group

Reporting group description:

Perioperative management of the patients according to the fast-track procedure (Novum) comprising pre- and postoperative measurement of the liver function by means of the LiMAx test. Therefore, the investigational medicinal product was administered twice. The postoperative LiMAx test was performed in the recovery room.

Reporting group title	Control group

Reporting group description:

Perioperative management of the patients according to the clinical standard of care (standard transfer practice based on defined treatment and diagnostic algorithms)

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized patients (n=148, LiMAx group: n=76, control group: n=72).

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The following patients were included in the modified Intention-to-treat population:
1. Randomised patients (control group).
2. Randomised patients with a postoperative LiMAx test (LiMAx group).
3. None of the following exceptions occurred:
 a. The planned liver resection was not done or was postponed for more than 72 hours.
 b. The required OPS code (5-502) was changed during surgery and/or surgery discontinued due to extended tumour progression.
 c. Death of patient during surgery.
 d. The planned liver resection had to be extended by an unplanned surgery concerning other solid organs.
 e. Leukocyte count was less than 1/nl before surgery (visit 4a).
 f. Elevated measures of ALT or AST, higher than 1000 units/l before surgery .

(n=118, LiMAx group: n=58, control group: n=60)

Primary: True positive subjects

End point title	True positive subjects

End point description:

Number of patients who were transferred to a general ward via the recovery room either due to positive result of the LiMAx test, or due to defined treatment or diagnostic criteria in the standard transfer practice, remained there and were able to be regularly discharged from the general ward at the latest on the 30th postoperative day.

End point type	Primary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative general ward assignment)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	60	118	
Units: Subjects				
True positive	36	1	37	
Other	22	59	81	

Statistical analyses

Statistical analysis title	True positive subjects
Comparison groups	LiMAx group v Control group
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: False positive subjects

End point title	False positive subjects

End point description:

False positive patients were those patients who were transferred to a general ward either due to the positive result of the LiMAx test, or due to the defined treatment or diagnostic criteria in the standard transfer practice, but could not be regularly discharged from there (e.g. due to transfer to the INT, no regular discharge after less than 30 days postoperatively, or death of the patient). Patients for whom a positive test result was revised following the evaluation of extrahepatic criteria by a physician in the recovery room were also considered as false positives.

End point type	Secondary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative decision for ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative decision)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	60	118	
Units: Subjects				
False positive	16	2	18	
Other	42	58	100	

Statistical analyses

Statistical analysis title	False positive subjects
Comparison groups	LiMAx group v Control group

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel

Notes:

[1] - It was expected, that the number of false positive subjects is higher in the LiMAx group, hence no superiority analysis was planned a-priori. The rates of both groups with their 95% confidence intervals were considered instead. For completeness, the CMH test was done.

Secondary: Specificity

End point title	Specificity

End point description:

The specificity was estimated by calculation of the following ratio per group:
number of true negatives/ (number of true negatives + number of false positives)
(probability that the test result is negative given the patient is not appropriate for transfer to a general ward).
Only true negative or false positive subjects of the mITT analysis set (53 subjects) are analysed.

End point type	Secondary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative decision for ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative decision)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18	35	53	
Units: Subjects				
True negative	2	33	35	
False positive	16	2	18	

Statistical analyses

Statistical analysis title	Specificity
Comparison groups	LiMAx group v Control group
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[2] - It was expected, that the number of false positive subjects is higher in the LiMAx group, hence no superiority analysis was planned a-priori. The rates of both groups with their 95% confidence intervals were estimated according to Pearson-Clopper. For completeness, the CMH test was done.

Secondary: Sensitivity

End point title	Sensitivity

End point description:

The sensitivity was estimated by calculation of the following ratio per group:
number of true positives / (number of true positives + number of false negatives)

(probability that the test result is positive given the patient really is appropriate for transfer to a general ward).
Only true positive or false negative subjects of the mITT analysis set (65 subjects) are analysed.

End point type	Secondary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative general ward assignment)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	25	65	
Units: Subjects				
True positive	36	1	37	
False negative	4	24	28	

Statistical analyses

Statistical analysis title	Sensitivity
Comparison groups	LiMAx group v Control group
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Positive predictive value

End point title	Positive predictive value

End point description:

The positive predictive value of tests was estimated by calculation of the following ratio per group:
number of true positives / (number of true positives + number of false positives)
(probability that a patient is suitable for transfer to a general ward given that the test result is positive)
Only true positive or false positive subjects of the mITT analysis set (55 subjects) are analysed.

End point type	Secondary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative general ward assignment)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	3	55	
Units: Subjects				
True positive	36	1	37	
False positive	16	2	18	

Statistical analyses

Statistical analysis title	Positive predictive value
Comparison groups	LiMAx group v Control group
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0253
Method	Cochran-Mantel-Haenszel

Notes:

[3] - It was expected, that the number of false positive subjects is higher in the LiMAx group, hence no superiority analysis was planned a-priori. The rates of both groups with their 95% confidence intervals were estimated according to Pearson-Clopper. For completeness, the CMH test was done.

Secondary: Negative predictive value

End point title	Negative predictive value

End point description:

The negative predictive value of tests was estimated by calculation of the following ratio per group: number of true negatives/ (number of true negatives + number of false negatives)
(probability that a patient is not appropriate for transfer to a general ward given that the result of the test is negative).
Only true negative or false negative subjects of the mITT analysis set (63 subjects) are analysed.

End point type	Secondary

End point timeframe:

Visit 5 (Primary postoperative transfer):
Destination after surgery (control group with preoperative ICU assignment) respectively transfer destination after recovery room (LiMAx group and control group with preoperative general ward assignment)

End point values	LiMAx group	Control group	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	57	63	
Units: Subjects				
True negative	2	33	35	
False negative	4	24	28	

Statistical analyses

Statistical analysis title	Negative predictive value
Comparison groups	LiMAx group v Control group
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1108
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening up to the closing visit on post-operative day 30. Persisting subsequent diseases should be documented up until the completion of the trial.

Adverse event reporting additional description:

Safety assessment is performed by ECGs, pulse, blood pressure measurement and laboratory parameters.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	LiMAx group

Reporting group description:

Perioperative management of the patients according to the fast-track procedure (Novum) comprising pre- and postoperative measurement of the liver function by means of the LiMAx test. Therefore, the investigational medicinal product was administered twice. The postoperative LiMAx test was performed in the recovery room.

Reporting group title	Control group

Reporting group description:

Perioperative management of the patients according to the clinical standard of care (standard transfer practice based on defined treatment and diagnostic algorithms)

Serious adverse events	LiMAx group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 76 (10.53%)	14 / 72 (19.44%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
PT: General physical condition abnormal			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Liver function test abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
PT: Abdominal wound dehiscence			

subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Vascular pseudoaneurysm			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Wound dehiscence			
subjects affected / exposed	0 / 76 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Post procedural bile leak			
subjects affected / exposed	0 / 76 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
PT: Hypertension			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Hypertensive crisis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
PT: Cardiac arrest			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Acute myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

PT: Bile duct stent removal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
PT: Syncope			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PT: Asthenia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Pyrexia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Multi-organ failure			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
PT: Abdominal pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PT: Pleural effusion			

subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Pulmonary embolism			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
PT: Renal failure			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
PT: Pain in extremity			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PT: Haematoma infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Wound infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PT: Abdominal abscess			
subjects affected / exposed	0 / 76 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	LiMAx group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 76 (81.58%)	58 / 72 (80.56%)	
Vascular disorders			
PT: Hypertension			
subjects affected / exposed	4 / 76 (5.26%)	3 / 72 (4.17%)	
occurrences (all)	4	3	
PT: Hypotension			
subjects affected / exposed	5 / 76 (6.58%)	4 / 72 (5.56%)	
occurrences (all)	5	4	
PT: Circulatory collapse			
subjects affected / exposed	3 / 76 (3.95%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
PT: Oedema peripheral			
subjects affected / exposed	4 / 76 (5.26%)	3 / 72 (4.17%)	
occurrences (all)	4	3	
PT: Impaired healing			
subjects affected / exposed	3 / 76 (3.95%)	4 / 72 (5.56%)	
occurrences (all)	3	4	
PT: Pyrexia			
subjects affected / exposed	5 / 76 (6.58%)	4 / 72 (5.56%)	
occurrences (all)	7	4	
PT: Pain			
subjects affected / exposed	7 / 76 (9.21%)	9 / 72 (12.50%)	
occurrences (all)	10	9	
PT: Fatigue			
subjects affected / exposed	1 / 76 (1.32%)	3 / 72 (4.17%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
PT: Pleural effusion			
subjects affected / exposed	6 / 76 (7.89%)	4 / 72 (5.56%)	
occurrences (all)	6	4	
PT: Dyspnoea			
subjects affected / exposed	2 / 76 (2.63%)	3 / 72 (4.17%)	
occurrences (all)	2	3	

PT: Cough			
subjects affected / exposed	2 / 76 (2.63%)	5 / 72 (6.94%)	
occurrences (all)	2	5	
PT: Pneumothorax			
subjects affected / exposed	1 / 76 (1.32%)	2 / 72 (2.78%)	
occurrences (all)	1	3	
PT: Respiratory failure			
subjects affected / exposed	0 / 76 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
Psychiatric disorders			
PT: Sleep disorder			
subjects affected / exposed	8 / 76 (10.53%)	6 / 72 (8.33%)	
occurrences (all)	8	7	
Investigations			
PT: C-reactive protein increased			
subjects affected / exposed	2 / 76 (2.63%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
PT: Body temperature increased			
subjects affected / exposed	4 / 76 (5.26%)	5 / 72 (6.94%)	
occurrences (all)	4	5	
PT: Blood bilirubin increased			
subjects affected / exposed	1 / 76 (1.32%)	3 / 72 (4.17%)	
occurrences (all)	1	3	
PT: Haemoglobin decreased			
subjects affected / exposed	0 / 76 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
PT: Procedural nausea			
subjects affected / exposed	9 / 76 (11.84%)	5 / 72 (6.94%)	
occurrences (all)	9	6	
PT: Post procedural constipation			
subjects affected / exposed	5 / 76 (6.58%)	5 / 72 (6.94%)	
occurrences (all)	5	5	
PT: Wound complication			
subjects affected / exposed	26 / 76 (34.21%)	21 / 72 (29.17%)	
occurrences (all)	26	21	

PT: Procedural pain			
subjects affected / exposed	25 / 76 (32.89%)	24 / 72 (33.33%)	
occurrences (all)	25	24	
PT: Wound dehiscence			
subjects affected / exposed	2 / 76 (2.63%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
PT: Procedural dizziness			
subjects affected / exposed	2 / 76 (2.63%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
PT: Post procedural bile leak			
subjects affected / exposed	2 / 76 (2.63%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
PT: Wound secretion			
subjects affected / exposed	0 / 76 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	4	
Cardiac disorders			
PT: Tachycardia			
subjects affected / exposed	1 / 76 (1.32%)	4 / 72 (5.56%)	
occurrences (all)	1	4	
PT: Bradycardia			
subjects affected / exposed	0 / 76 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
Nervous system disorders			
PT: Dizziness			
subjects affected / exposed	7 / 76 (9.21%)	11 / 72 (15.28%)	
occurrences (all)	9	11	
PT: Hypoaesthesia			
subjects affected / exposed	4 / 76 (5.26%)	2 / 72 (2.78%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
PT: Anaemia			
subjects affected / exposed	3 / 76 (3.95%)	5 / 72 (6.94%)	
occurrences (all)	3	5	
PT: Leukocytosis			
subjects affected / exposed	4 / 76 (5.26%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
PT: Thrombocytopenia			

subjects affected / exposed	1 / 76 (1.32%)	4 / 72 (5.56%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
PT: Vomiting			
subjects affected / exposed	12 / 76 (15.79%)	10 / 72 (13.89%)	
occurrences (all)	15	11	
PT: Nausea			
subjects affected / exposed	17 / 76 (22.37%)	21 / 72 (29.17%)	
occurrences (all)	18	23	
PT: Constipation			
subjects affected / exposed	12 / 76 (15.79%)	9 / 72 (12.50%)	
occurrences (all)	13	9	
PT: Abdominal pain			
subjects affected / exposed	3 / 76 (3.95%)	4 / 72 (5.56%)	
occurrences (all)	3	6	
PT: Abdominal distension			
subjects affected / exposed	6 / 76 (7.89%)	6 / 72 (8.33%)	
occurrences (all)	6	6	
PT: Diarrhoea			
subjects affected / exposed	0 / 76 (0.00%)	3 / 72 (4.17%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
PT: Hyperhidrosis			
subjects affected / exposed	2 / 76 (2.63%)	3 / 72 (4.17%)	
occurrences (all)	2	3	
PT: Pruritus			
subjects affected / exposed	0 / 76 (0.00%)	4 / 72 (5.56%)	
occurrences (all)	0	4	
PT: Erythema			
subjects affected / exposed	0 / 76 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
PT: Musculoskeletal pain			
subjects affected / exposed	6 / 76 (7.89%)	5 / 72 (6.94%)	
occurrences (all)	6	6	
PT: Back pain			

subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 6	6 / 72 (8.33%) 6	
Infections and infestations PT: Urinary tract infection subjects affected / exposed occurrences (all)	 4 / 76 (5.26%) 4	 4 / 72 (5.56%) 4	
Metabolism and nutrition disorders PT: Hypoalbuminaemia subjects affected / exposed occurrences (all) PT: Hypokalaemia subjects affected / exposed occurrences (all)	 2 / 76 (2.63%) 2 12 / 76 (15.79%) 12	 3 / 72 (4.17%) 3 8 / 72 (11.11%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2013	Substantial Amendment submitted 23 August 2013 due to the suggested amendments between study protocol Version 04 dated November 05, 2012, and study protocol Version 05, dated August 15, 2013. The protocol was amended for the following reasons: - Prolongation of study recruitment time line - Rewording of inclusion/exclusion criteria for clarification - Update on participating investigators/study sites - Changes related to revised scheduling of visit 4 (separated with protocol version 05 into visit 4a and 4b). Due to the separation into steps 4a and 4b it was ensured that the safety blood draw 12 – 24 hours after the last application of the investigational medicinal product was still conducted (4a) within this time frame, whereas the volumetry of the resectate was able to be conducted at the day of the surgery (4b) even if the surgery takes place 72 hours later. - Adjustment of the time frame for conduct of the postoperative LiMAx test up to 6 hours after skin suturing. - Premature withdrawal: Clarification which type of organs that might have been affected by an expansion of the surgery might result in a premature drop out of the patient. Clarification was focusing on organ types potentially increasing the postoperative risks.
20 March 2014	Substantial Amendment submitted 11 March 2014 due to the suggested amendments between study protocol Version 05 dated August 15, 2013, and study protocol Version 06, dated March 03, 2014. The protocol was amended for the following reasons: - Prolongation of study recruitment time line - Rewording of inclusion/exclusion criteria for clarification - Update on participating investigators/study sites

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported