SYNOPSIS

Name of Sponsor/Company: Humedics GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: ^{13}C-Methacetin Solution for Infusion		
Name of Active Ingredient: 0.4% ^{13}C-Methacetin Solution		
Title of Study: 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		
Investigator(s): PD Dr. med. Martin Stockmann, Prof. Dr. Utz Settmacher, Dr. Hans-Michael Tautenhahn, Dr. Johan Friso Lock, Dr. Jens Mittler, Prof. Dr. Hueseyin Bektas		
Study centres: 6 sites in Germany		
Publication (reference): None		
Studied Period*:* First patient in: 23.01.2013 Last patient out: 01.09.2015	**Phase of Development:** III	

Objectives:

The main purpose was to demonstrate efficacy, safety and benefit/risk analysis of the intravenously administered ^{13}C-Methacetin Solution for Infusion as a diagnostic agent for the measurement of liver function according to the LiMAx (Liver Maximum Capacity test) procedure compared to an untreated control group in patients undergoing partial liver resection. The control group represented the clinical standard of care.

The primary intention was to show the benefit of this diagnostic procedure for the patient by influencing the clinical practice 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.

As decisive target parameter for the decision on the postoperative management under the fast-track procedure a postoperative LiMAx value of >150 µg/kg/h was to be established as a valid and safe cut-off value for the diagnostic agent.

Methodology:

This was a prospective, randomised, controlled, multi-centre Phase III study for the clinical investigation of ^{13}C-Methacetin Solution for Infusion as diagnostic agent in the LiMAx test in patients undergoing partial liver resection. The LiMAx test comprised of the application of the diagnostic agent ^{13}C-Methacetin Solution for Infusion and a breath test using the LiMAx procedure for the determination of liver function.

The study consisted of two arms:

LiMAx group: 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.

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

(**comparator**). In this group no LiMAx test was performed and therefore the investigational medicinal product was not administered. Also no placebo or comparator treatment was applied.

The LiMAx group (Novum) was compared to the clinical standard (control group). Perioperative management included preoperative planning of the surgery by the surgeon inclusive of planning for the primary transfer of the patient after surgery. The primary transfer was completed when the patient had been transferred for the first time to a general ward via recovery room or a unit with intensive monitoring (**INT** = Intensive station, INT – Intensive Care Unit/Intermediate Care Unit, monitoring station, waking station and other centre specific designations (corresponding to: = not a general ward, not a recovery station/room)).

The postoperative management after partial liver resection represented the decisive criterion, especially the primary transfer after the surgery.

In line with the usual **standard transfer practice** (represented by the control group), the following types of primary, postoperative transfer could be differentiated. These primary transfers were specified by the surgeon preoperatively on preparation of the surgery schedule.

- Primary transfer to INT:
  - directly from the surgical theatre
- Primary transfer to a general ward (= general ward indication):
  - only after stay in a recovery room
  - In recovery room: Evaluation whether a transfer to general ward was still indicated. If not, the preoperatively taken decision for primary transfer was revised and a transfer to INT was performed

Control group (standard transfer practice): In line with current usual perioperative management, the primary postoperative transfer was pre-specified by the surgeon during the planning of the surgery, taking into account all available information about the patient up to this time. For patients with the option of a primary transfer to a general ward as specified in the surgery schedule (test positive), it was verified during the stay in the recovery room whether a transfer to a general ward was still indicated. In the positive case a transfer to a general ward took place. In case of a negative assessment (especially judged by extrahepatic criteria), the original decision specified in the surgery schedule was revised and these patients were transferred to INT. If a direct transfer from the surgical theatre to INT was specified in the surgery schedule (test negative), a further evaluation of the condition of the patient was performed only after completion of this primary transfer to INT.

LiMAx group: In a modification of the clinically common standard transfer practice, all patients in the LiMAx group were primarily transferred either to INT or to the general ward via the recovery room with the fast-track procedure.
For these patients, the determination of a general ward indication took place in the recovery room, when a postoperative LiMAx value >150 µg/kg/h was achieved (test positive) and postoperative clinical extrahepatic criteria allowed a transfer to the general ward. For LiMAx values ≤150 µg/kg/h no general ward indication was present and a transfer to INT took place (test negative).

Assessment of the correctness of the prediction of the primary transfer:
The correctness of the prediction for the primary transfer to INT, as well as to the general ward was verified retrospectively, respectively over the progression via the following procedures:

The necessity, and thereby the correctness of the primary transfer to INT (test negative) was retrospectively assessed in both groups. For this the postoperatively recorded patient data of all test negative patients who were primarily transferred to INT were assessed in a blinded procedure by an independent committee ("*adjudication committee*"), which either confirmed or rejected the necessity/correctness of the intensive care allocation.

Furthermore, based on the study documentation for all test positive patients it was verified whether the following criteria were observed to substantiate the correctness of the primary transfer to the general ward:

- Up to regular discharge no transfer to INT had taken place
- Patient was regularly discharged before or at the latest on the postoperative day 30
- No death of the patient

On the basis of these specifications the patients were assigned to the following subgroups:

- **True positive patients:** True positive patients were all those 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.
- **False positive patients:** 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.
- **True negative patients:** True negative patients were all those who were transferred to INT either due to negative result of the LiMAx test, or due to defined treatment or diagnostic criteria in the standard transfer practice, and for whom retrospective evaluation by the group-blinded adjudication committee confirmed that allocation to INT was clinically appropriate.
- **False negative patients:** False negative patients were those patients who were transferred to INT either due to negative result of the LiMAx test, or due to defined treatment or diagnostic criteria in the standard transfer practice, and for whom retrospective evaluation by the group-blinded adjudication committee concluded that allocation to INT was not clinically necessary.

Number of patients:
Planned: 120, 60 each treatment group
Randomised: 148
Efficacy analysis: 118

Diagnosis and main Criteria for inclusion:
Key inclusion criteria

- Male or female patients ≥ 18 years, who were scheduled for partial surgical liver resection (at least segment resection, corresponding to operation and procedure key (OPS) coding 5-502; this means that a resection of at least one or more segments, if applicable also atypical) was planned. Including all benign and malignant tumour entities (e.g. focal nodular hyperplasia, liver cell adenoma, hepatocellular carcinoma, cholangiocellular carcinoma, liver metastases).
- Patients for whom a thin-layer computer tomography (CT) or a magnetic resonance

imaging (MRI) of the liver was planned before surgery, or for whom a preoperative thin-layer CT or an MRI of the liver was available not older than 6 weeks (for patients with malignant tumours) or not older than 3 months (for patients with benign diseases).
- Signed written informed consent after explaining the nature of the study.

Key exclusion criteria
- Anamnestically known hypersensitivity towards one of the used medicines or their ingredients, or towards medicines with similar chemical structure (especially Paracetamol intolerance/ allergy)
- Patients who had received an open or laparoscopic partial liver resection corresponding to at least one segment resection (OPS-Code 5-502) (including biliodigestive anastomosis, exclusive cholecystectomy).
- Patients with severe cardiovascular and/or severe diseases of the respiratory system, who require postoperative intensive monitoring per se (e.g. status after heart surgery, bypass, valve replacement, unstable Angina Pectoris, severe coronary heart diseases with intervention in the last 6 months, severe COPD (chronic obstructive pulmonary disease), severe asthma with continuous oral cortisone medication)

Test product, dose and mode of administration, batch number:
Investigational medicinal product for LiMAx group:
- 0.4% ^{13}C-Methacetin Solution for Infusion
- Dosage: 2 mg/kg body weight-adjusted
- Application form: Intravenous
- Frequency: 1 x before surgery, 1 x after surgery

The batch numbers of ^{13}C-Methacetin Solution utilised throughout the study were 241072, 330051 and 330069.

Duration of Treatment:
Not applicable (bolus application; maximum 20 sec)

Reference therapy:
Control group (standard transfer practice)
No application of placebo or comparator was performed.

Criteria for Evaluation
Efficacy:
Primary parameter:
- Number of the true positive patients in each treatment group

Secondary parameters:
- Number of the false positive patients
- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Number of the patients with postoperative liver failure (PHLF, post hepatectomy liver failure)
- Total rate of complications
- Total mortality

Tertiary parameter:
- Evaluation of correlation between residual liver function (RLF) and residual liver volume (RLV) based on preoperative liver and tumour volumetry (CT or MRI based), intraoperative volumetric analysis of the resected liver portions and pre- and postoperative determination of LiMAx values.

Safety:

- Adverse events (AEs)
- Vital signs
- Laboratory evaluation
- Electrocardiograms (ECG)

Statistical Methods:

In this study the changed perioperative management in the fast-track procedure through the LiMAx test (Novum) was tested against the usual clinical standard (comparator) in a multi-centre, confirmatory study. The primary objective of the study was to demonstrate that the LiMAx test validly and safely identifies those patients who were able to be transferred immediately postoperatively to a general ward via the recovery room based on a LiMAx cut-off value of >150 µg/kg/h. The correctness of the prediction of both test procedures was tested over the progression (transfer/regular discharge in the test positive group), respectively by retrospective evaluation (by committee in the test negative group). The tests were applied in two independent treatment groups (LiMAx/control). The plan was to recruit n=60 patients per study arm. The randomisation to both study arms was stratified and took place in the ratio 1:1.
The primary target criterion was the success rate of the true positive patients in both groups. The superiority of the LiMAx test was tested against the clinical standard of care as represented by the control group. The analysis was stratified according to centre using Cochran-Mantel-Haenszel test. The most important secondary target criteria were the diagnostic parameters (sensitivity, specificity, positive predictive value, negative predictive value), which were analogously assessed. Relevant for the analyses was a defined mITT (*modified Intention-To-Treat*) population. No interim analyses were planned.

Key Analysis Subgroups:

- <u>Safety population (148 patients):</u>
  Includes all randomised patients.
  As predefined in the protocol, randomised patients with surgery-related exceptions (e.g. cancellation of surgery; discontinuation of surgery due to extended tumour progression) where not considered in the following two key efficacy analysis populations:
- <u>mITT population (118 patients):</u>
  Includes all patients of the LiMAx group of the efficacy analysis population with available postoperative LiMAx value (58 patients) as well as all control group patients (60 patients) of the efficacy analysis population.
- <u>Subgroup I of the mITT population (100 patients):</u>
  Subgroup of the mITT population which excludes all false positive patients for whom the postoperative patient management was due to the evaluation of extrahepatic criteria and not based on the test result. Therefore, in the subgroup I analysis16 test positive patients of the LiMAx and 2 test positive patients of the control group, for whom the test result was overruled by the responsible physician in the recovery room due to the occurrence of extrahepatic criteria were not considered.

Efficacy Results:

<u>Primary endpoint:</u>

- The rate of true positive patients was significantly higher in the LiMAx group as compared to the control group (62.1 % [n=36] vs. 1.7 % [n=1], $p<0.0001$). When considering subgroup I of the mITT population, which excluded 18 patients (16 LiMAx group patients, 2 control group patients) transferred to INT due to extrahepatic criteria, the rate of true positives in the LiMAx group was also higher as compared to the control group (85.7 % [n=36] vs. 1.7 % [n=1], $p<0.0001$). Therefore, the primary endpoint was met and superiority of the LiMAx test to standard transfer practice was

proven.

Secondary endpoints:

- The rate of false positive patients was significantly higher in the LiMAx group as compared to the control group (27.6 % vs. 3.3 %, p=0.0002). This inferiority was expected due to the study design. Due to the conservative nature of the standard transfer practice, which assigned 69 out of 72 patients in the control group (safety population) to INT, there remained only 3 patients assigned to the general ward; 2 of these turned out to be false positives. In contrast, for the LiMAx group, 52 of 58 patients (mITT) had a positive test result; of these 16 turned out to be false positives due to the occurrence of extrahepatic criteria assessed in the recovery room. When these patients were excluded from the analysis (subgroup I of the mITT population), the rate of false positive patients was equal in both groups (0.0 %).
- The sensitivity was significantly higher in the LiMAx group as compared to the control group (90.0 % vs. 4.0 %, p<0.0001). Therefore, this secondary endpoint was met and superiority of the LiMAx test to standard transfer practice was proven.
- The specificity was significantly lower in the LiMAx group as compared to the control group (11.1 % vs. 94.3 %, p<0.0001). This inferiority was expected due to the study design. For subgroup I of the mITT population, which excluded patients rated as false positive due to the occurrence of extrahepatic criteria, the specificity rose to 100 % in both groups.
- The positive predictive value was significantly higher in the LiMAx group as compared to the control group (69.2 % vs. 33.3 %, p=0.0253). For subgroup I of the mITT population, positive predictive value is equal in both groups (100.0 %).
- The negative predictive value was numerically lower in the LiMAx group as compared to the control group (33.3 % vs. 57.9 %), but this difference was not statistically significant (p=0.1108). This secondary endpoint was not met. Retrospectively, overall only few LiMAx patients (n=6; control group: n=57) were test negative and among those the majority was false negative (n=4; control group: n=24).
- Due to the low number of patients with posthepatectomy liver failure (LiMAx group: n=1; control group: n=1), statistical evaluation of this secondary endpoint was highly affected by the imputation of missing values as posthepatectomy liver failure (LiMAx group: 6 missing values; control group: 12 missing values) and was therefore not considered to be meaningful.
- The rate of severe complications was significantly lower in the LiMAx group as compared to the control group (13.8 % vs. 31.7 %; p=0.0072).
- The mortality rate was lower in the LiMAx group as compared to the control group (0 % vs. 5 %), but narrowly failed to be statistically significant (p=0.0538).

Tertiary endpoint:

A significant correlation (r=0.6051, p<0.0001) was observed between residual liver volume and residual liver function as determined by the LiMAx test.

Safety Results:

^{13}C-Methacetin Solution for Infusion was well tolerated following the pre- and postoperative administrations of 2 mg/kg body weight within the LiMAx test.

There was no safety signal associated with the i.v. administration of ^{13}C-Methacetin Solution for Infusion preoperatively nor in the more critical postoperative situation. The types of AEs and SAEs were similar between the two study groups. Only 1 possibly related AE was observed (nausea). This AE was of mild intensity and recovered the same day without intervention. There were no clinically relevant or unexpected findings in vital signs, ECG and clinical laboratory tests. These safety conclusions are applicable to all the subpopulations

evaluated.

Conclusion:

The primary efficacy analysis demonstrated the clinical benefit of the diagnostic agent ^{13}C-Methacetin Solution for Infusion administered during the LiMAx test to provide information beneficial for the patient by increasing the portion of patients transferred to general ward after surgery as compared to standard transfer practice, without compromising patient safety. The safety of the LiMAx test was demonstrated by the fact that there were no false positive patients due to insufficient liver function. All false positive patients were transferred to INT due to extrahepatic criteria as determined by the physician in the recovery room. A sensitivity of 90 % (compared to 4 % in standard transfer practice), and a specificity as well as a positive predictive value of 100 % (subgroup 1, i.e. excluding the 18 patients transferred to INT due to extrahepatic criteria, representing all false positive patients) reflect the diagnostic performance of the LiMAx test and the impact on diagnostic thinking by providing a significantly higher probability of a correct diagnosis after the test than without the test.

The LiMAx test provides information on the prognosis that is independent from other data of the conventional work-up. Moreover, it has been demonstrated that the LiMAx test can replace independent prognostic factors which are more demanding to obtain (e.g. static laboratory results and scoring systems derived thereof). False positive results leading to an inappropriate transfer of an INT patient to the general ward were not observed (subgroup I, i.e. excluding patients transferred to INT due to extrahepatic criteria). The negative predictive value was lower in the LiMAx group than in the control group, indicating that the chosen cut off of >150 µg/kg/h was conservative enough to exclude the potential risk of incorrectly transferring an INT patient to the general ward.

Taken together, the LiMAx test validly identified patients with a sufficient liver status suitable for a primary postoperative transfer from the recovery room to the general ward and may become a standard procedure where quantitative assessment of liver function can have an impact on patient management.

In line with literature, the pre- and postoperative i.v. administration of 2 mg/kg body weight ^{13}C-Methacetin Solution for Infusion was safe and well-tolerated in patients undergoing partial liver resection. Clinically relevant related AEs or ECG changes were not observed.

Date of the Report: 18 MAR 2016