Clinical Investigation Plan

According § 47 MPDG in conjunction with Art. 82 MDR

Title:	**He**pato**r**enal Syndr**o**me-acute kidney injury (HRS-AKI) treatment with transjugular intrahepatic portosystemic shunt in patients with cirrhosis. A randomized controlled trial
Acronym:	Liver-HERO
Identification No acc. to § 48 (3) MPDG:	DE-22-00013779
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Protocol Version, Date:	Final V01 of 03-AUG-2022
Sponsor	Friedrich-Schiller-University Jena 07737 Jena
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Confidential statement:

The information in this trial protocol is strictly confidential. It is for the use of the sponsor, investigator, trial personnel, ethics committee, competent authorities and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the sponsor or the Principal Coordinating Investigator (PCI).

Please note that in this study protocol a reference to a particular gender is a reference to all genders.

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1 General

1.1 Synopsis

Study Title	**He**pato**r**enal Syndr**o**me-acute kidney injury (HRS-AKI) treatment with transjugular intrahepatic portosystemic shunt in patients with cirrhosis. A randomized controlled trial.
Short Title	Liver-HERO
Sponsor	Friedrich-Schiller-University Represented by the Dean of the Medical Faculty Who is represented by the Principal Coordinating Investigator Prof. Dr. Cristina Ripoll University Hospital Jena, Clinic for Internal Medicine IV (Gastroenterology, Hepatology, Infectiology, Interdisciplinary Endoscopy) Am Klinikum 1, 07747 Jena
Indication	Hepatorenal syndrome-acute kidney injury (HRS-AKI) in patients with cirrhosis
Study Population	Patients with cirrhosis with ascites and HRS-AKI
Medical Device under Investigation	Gore® Viatorr® Controlled Expansion® Endoprosthesis Transjugular intrahepatic portosystemic shunt, CE-certified
Primary Objective	To evaluate if a transjugular intrahepatic portosystemic shunt (TIPS) implantation in patients with HRS-AKI improves survival.
Secondary Objectives	To evaluate whether TIPS implantation in patients with HRS-AKI • improves renal function • improves Health-related Quality of Life (HrQoL) • has an impact on development of liver cirrhosis complications
Study Design	Prospective, multicenter, randomized controlled parallel-group study Randomization: 1:1 Blinding: open Stratification: site and AKI stage
Study Treatment	**Experimental group:** transjugular intrahepatic portosystemic shunt (TIPS) **Control group**: Standard of care (terlipressin and albumin)
Further study specific measures	• Questionnaires (SF-36, CLDQ) • Biosamples (Blood, urine; optional: stool)
Primary Endpoint	12-month Liver transplant-free survival
Secondary Endpoints	1. 3-month liver transplant-free survival 2. Indication for TIPS placement or TIPS revision during follow-up 3. Development of further decompensation during follow-up 4. Reversal of HRS-AKI at 3 and 12 months (vs. baseline), defined as return of serum creatinine level to ≤ 0.3 mg/dl (26.5 µmol/L). 5. Partial response to treatment at 3 and 12 months (vs. baseline), defined as reduction of at least one AKI stage with decrease of serum creatinine to ≥ 0.3 mg/dl (26.5 µmol/L) above the baseline value. 6. In-hospital, 28-day and 90-day survival. 7. Length of in-hospital-stay 8. Relative changes in HrQoL (as measured by SF-36 and CLDQ) at 3 and 12 months (vs. baseline) 9. Need for renal replacement therapy 10. Recurrence of HRS-AKI after treatment at 3 and 12 months 11. Development of acute-on-chronic liver failure during follow-up 12. Impact of the presence of intrinsic nephropathy as assessed by cystatin C and UnGAL on outcomes 13. Association of pathophysiological mechanisms of cirrhosis with outcomes (in further studies) 14. **Assessment of safety:** Number of AEs and SAEs in each group with special attention on ischemic hepatitis, the development of acute on chronic liver fail-

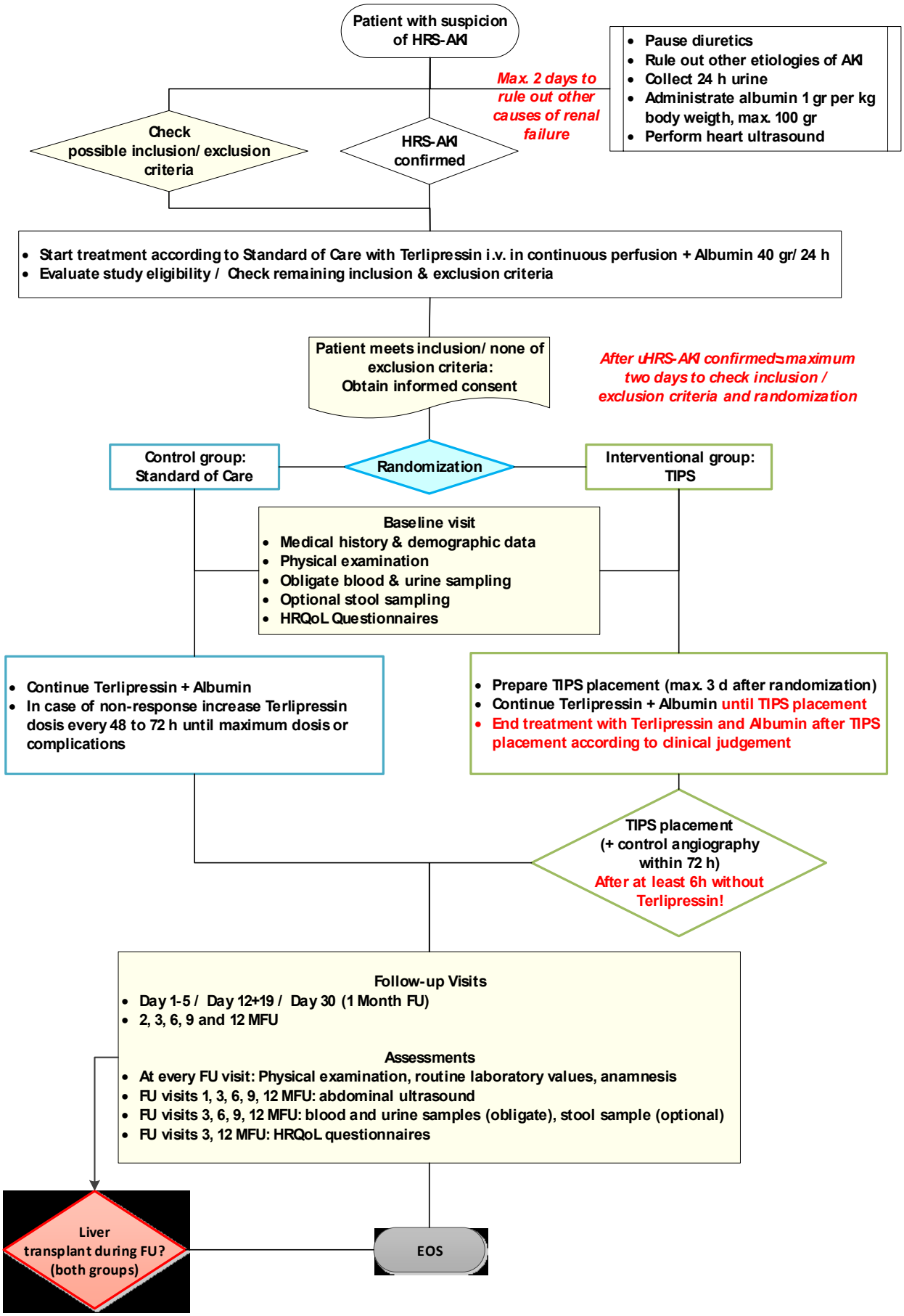
	ure and signs of heart failure. Laboratory assessments include sodium, potassium, ALAT, ASAT, GGT, AP, bilirubin, albumin and INR and will be analysed descriptively as safety parameters.
Inclusion criteria	1) Patients with cirrhosis confirmed by histology or liver stiffness or with unequivocal signs in ultrasound, endoscopy and/or blood tests 2) Clinically evident ascites due to portal hypertension (SAAG > 1.1 g/dL) 3) HRS-AKI stages 2 or 3 4) Planned vasoactive treatment for the management of HRS, as defined by the administration of terlipressin + albumin 5) Age: ≥ 18 to ≤ 75 years old at the time of consent 6) ECOG < 4 prior to hospital admission 7) Subject has been informed of the nature of the study, is willing to comply with all required follow-up evaluations within the defined follow-up visit windows and has signed an Ethics Committee (EC) approved consent form. 8) Female subjects of childbearing potential have a negative pregnancy test ≤ 7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation. Female subjects will be exempted from this requirement in case they are sterile, infertile, or have been post-menopausal for at least 12 months (no menses). A contraceptive method with a pearl index below 1% is assumed to be effective.
Exclusion criteria	1) Patients with signs of intrinsic renal disease as defined by proteinuria (> 500 mg per day), microhematuria (> 50 RBC per high power field) or signs of chronic renal disease on ultrasound. 2) Recent or current use of nephrotoxic drugs (NSAIDS, Aminoglycosides or iodinated contrast medium) in the previous 72 hours before AKI diagnosis 3) Improvement of renal function after 2 days of diuretic removal and plasma volume expansion with albumin 1 gr/kg 4) Uncontrolled shock 5) Patients with uncontrolled infection (defined by a 20 % increase in inflammatory parameters (CRP, leucocytes or insufficient decrease of PMN in ascitic fluid < 25 % from baseline in the case of a SBP) despite 48 hours of antibiotic treatment. 6) Patients with cardiac cirrhosis as defined by the development of cirrhosis in a patient with chronic heart failure due to a primary cardiac disease (ischemic cardiomyopathy, hypertensive cardiomyopathy, etc.) 7) Patients with contraindications to TIPS placement (Bilirubin > 5 mg/dL, recurrent hepatic encephalopathy) 8) Patients with cavernous portal vein thrombosis, splenic vein thrombosis or mesenteric vein thrombosis 9) Patients with clinically significant cardiac disease (NYHA ≥ II) 10) Patients with diastolic dysfunction grade 3. 11) Patients with a reduced systolic function with an ejection fraction ≤ 50 % 12) Patients with an acute variceal bleeding at the time of screening who have indication for pre-emptive TIPS and/or terlipressin. 13) Patients with refractory ascites as defined by the International Ascites Club (< 800 gr weight loss over 4 days in patients on low salt diet and high dose diuretics (spironolactone 400 mg /day and furosemide * 160 mg /day), or lower dose of diuretics with complications secondary to the use of diuretics such as hyponatremia, renal failure, hepatic encephalopathy. *equivalent dose of torasemide 40 mg/day 14) Patients with hepatocellular carcinoma outside of the Milan criteria 15) Patients with hepatocellular carcinoma within the Milan criteria in whom the tumor is located in the puncture tract. 16) Patients with benign liver tumors (except regenerative nodules) which are located in the puncture tract. 17) Patients with other comorbidities that lead to an estimated life expectancy under 1 year.

	18) The subject is currently enrolled in another investigational device or drug trial. 19) Patients with pregnancy or lactation
Number of Sites	Approximately 10-15 sites in Germany
Number of Subjects	**To be assessed for eligibility: n = 230** **To be assigned to the trial, i.e. recruited: n = 124 (62 per arm)** **To be analyzed: n = 112 (56 per arm)** Dropout rate of 10% expected.
Schedule	**Study related:** Planned Start date: Q3/2022 Planned Duration of enrolment: 24 months Estimated end date: Q3/2026 **Duration of intervention per patient:** The procedure of the TIPS implantation (interventional group only) takes approximately 2 hours. This device is then permanently implanted. **Follow-up per patient:** 12 months (13 on-site visits: days 1-5, 12, 19 and 1, 2, 3, 6, 9 and 12 months)
Statistical analysis	**Statistical methods used to compare groups for primary and secondary outcomes:** The primary endpoint will be analyzed based on the intention-to-treat (ITT) principle using a Cox regression adjusted for AKI stage. Drop-outs will be dealt with as independent right censored in the primary analysis. All patients will be analyzed in their randomization-group. A per-protocol analysis will be performed as sensitivity analysis of the primary outcome. Drop-outs and C-to-T-switcher will be dealt with as independent right censored in this analysis without T-to-C-switchers (T = TIPS group, C = control group). Additional both analyses will be performed with requirement of TIPS implantation/revision in the follow-up as third endpoint. A Competing-Risk-Analysis in addition to the primary endpoint with the competing events death and liver transplantation will be performed. Reversal of HRS-AKI (vs baseline), partial response to treatment (vs baseline), need of renal replacement therapy and recurrence of HRS-AKI at 3 and 12 months will be assessed by logistic regression adjusted for AKI stage. In-hospital, 28-day and 90-day survival will be assessed by logistic regression adjusted for AKI stage. Changes in HrQoL at 3 and 12 months with respect to study baseline will be compared between groups by linear regression adjusted for AKI stage. 3-month liver transplant free survival will be analyzed using a Cox regression adjusted for AKI stage. Development of further decompensations and Length of in-hospital-stay will be analyzed descriptively. Results will be interpreted in an exploratory manner. **Methods for additional analyses, such as subgroup analyses and adjusted analyses:** Effects (centers, presence/absence of intrinsic renal damage as determined by plasma and urine biomarkers, etiology of the underlying liver disease (alcoholic versus non-alcoholic)) and impact of the presence of intrinsic nephropathy (as assessed by cystatin C and UnGAL) will be checked with BIC. In case of significance, results will be interpreted in an exploratory manner.
Funding	German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) Funding number: 431667134 Reference number: RI 3205/1-1

1.2 Abbreviations

ACLF	Acute-on-chronic liver failure
ADE	Adverse Device Effect
AE	Adverse event
AESI	Adverse events of special interest
AKI	Acute kidney injury
ALAT	alanine aminotransferase
AP	Alkaline phosphatase
ASAP	As soon as possible
ASAT	Aspartate aminotransferase
BIC	Bayesian information criterion
BCLC	Barcelona Clinic Liver Cancer classification
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
BfS	Bundesamt für Strahlenschutz (German Federal Office for Radiation Protection)
C	Control group
CA	Competent Authority
CI	Confidence interval
CIP	Clinical investigation plan
CKD	Chronic kidney disease
CLDQ	Chronic liver disease questionnaire
CM	Contrast medium
CPG	Clinical practice guidelines
CRA	Clinical research associate
CRF	case report forms
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFG	Deutsche Forschungsgemeinschaft
DMIDS	Deutsches Medizinprodukte-Informations- und Datenbank-System
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of Liver Diseases
EBL	Endoscopic band ligation
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOS	End of study
EOT	End of Treatment
ePTFE	Expanded Polytetrafluorethylen
FU	Follow up
GCP	Good Clinical Practice
GDPR	General data protection regulation
GGT	Gamma-glutamyltransferase
Gy	Gray
HCC	Hepatocellular cancer
HR	Hazard ratio
HrQoL	Health-related Quality of Life
HRS	Hepatorenal syndrome
IAC	International Ascites Club
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use (Gebrauchsanleitung)
IMP	Investigational Medicinal Product
INR	International normalized ratio
ISF	Investigator Site File
ITT	Intention to Treat
KDIGO	The Kidney Disease: Improving Global Out-comes
KKS	Koordinierungszentrum für Klinische Studien (Coordinating Center for Clinical Studies)
LA	Left atrium
LtFU	Lost to Follow up
LTX	Liver transplantation
LV	Left ventricle
MAP	Mean arterial pressure
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation (VO (EU) 2014/745)
MedDRA	Medical Dictionary for Regulatory Activities
MPDG	Medizinprodukterecht-Durchführungsgesetz
NAKI	Non Acute Kidney Injury
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
OS	Overall survival
PC	Post-contrast
PMN	Polymorphonuclear leukocytes
PP	Per protocol
PTFE	Polytetrafluoroethylene
RAAS	renin-angiotensin-aldosterone system
RBC	Red blood cells
RTC	Randomized controlled trial
SAAG	Serum-Ascites-Albumin-Gradient
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SBP	Spontaneous bacterial Peritonitis
sCr	Serume creatinine
SF36	Short Form 36 (Health questionnaire)
SoC	Standard of Care
Sv	Sievert
T	TIPS group
TIPS	transjugular intrahepatic portosystemic shunt
TMF	Trial Master File
TR	tricuspid regurgitation
UADE	Unexpected ADE
uETG	urinary ethyl glucuronide
uNGAL	Urine neutrophil gelatinase-associated lipocalin
USADE	Unexpected serious ADE
ZKS	Zentrum für Klinische Studien (Center for Clinical Studies)

1.3 Flow Chart



1.4 Visit Schedule

	Pre-Screening **within SoC** / confirmation of HRS-AKI diagnosis	Screening / Baseline	FU Day 1-5	FU Day 12 and 19	FU Day 30 (1 MFU)	FU 2 Months (2 MFU)	FU 3 Months (3 MFU)	FU 6 and 9 months (6 MFU, 9 MFU)	FU 12 Months (12 MFU)
Medical history / Anamnesis[1]	X	X							
Demographic data		X							
Physical examination[2]	X	X	X	X	X	X	X	X	X
Routine laboratory examination [3]	X		X	X	X	X	X	X	X
24h urine	X				X				
uETG / alcohol consumption		X		X	X	X	X	X	X
Echocardiography	X								
Abdominal ultrasound	X				X		X	X	X
Diagnostic paracentesis	X								
Chest-X-Ray	X								
Inclusion / Exclusion criteria		X							
ICF		X							
Randomization		X							
Blood and urine sampling		X					X	X	X
Optional stool sampling		X					X	X	X
Terlipressin / Albumin treatment[4]		X	#						
TIPS		X	An-gio[5]						
HrQoL Questionnaires (SF-36, CLDQ)		X					X		X
AE/SAEs		X							
Length of in hospital stay		X							
Liver transplantation performed		X							
Requirement of Renal replacement therapy		X							

Total: 13 follow-up visits, all conducted on-site.

[1] Medical history / Anamnesis includes questions on occurrence of HCC, medication intake, actual status of HRS-AKI/ascites (previous and actual therapies/measures, decompensation), intake of low-salt diet

[2] Physical examination includes: Evaluation of orientation (time, person, place) and presence of flapping tremor, Evaluation of skin, Heart and lung auscultation, abdominal physical examination, presence of lower limb edema

[3] Laboratory values (assessed by local lab): 1) in blood: creatinine, sodium, potassium, ALAT, ASAT, GGT, AP, Bilirubin, Albumin, CRP, INR, hemoglobin, hematocrit, leukocytes, platelets, 2) in ascites/pleural effusion; albumin, leukocytes, neutrophils, glucose, LDH, bilirubin.

[4] For interventional arm until TIPS placement and then will be progressively discontinued according to the managing physician's decision. For SoC arm the treatment will be given beyond baseline (#), and continued according to the Clinical Practice Guidelines and the managing physician's decision.

[5] Control angiography within 72 hours after TIPS placement (measurement should be performed after pausing Terlipressin for at least 6 hours)

2 Medical Background

Liver cirrhosis is a major cause of global health burden with 31 million disability adjusted life years and 1 million deaths worldwide in 2010 (Mokdad et al. 2014). In the natural history of liver disease, there are two clearly distinct clinical phases (D'Amico, Garcia-Tsao, and Pagliaro 2006; de Franchis et al. 2022). First, in the compensated phase, the patient is asymptomatic or oligosymptomatic. These patients have no symptoms of the disease although they may have signs of cirrhosis such as varices, spider naevi or blood test abnormalities. These patients have median survival of about 15 years (D'Amico, Garcia-Tsao, and Pagliaro 2006). During the course of the disease, the patients develop ascites, variceal bleeding or hepatic encephalopathy, which marks the transition to the decompensated phase of the disease (de Franchis et al. 2021).Patients who transition to the decompensated phase have a marked reduction in estimated survival with a median of approximately 2 years (D'Amico, Garcia-Tsao, and Pagliaro 2006). One of the main drivers of the development of decompensation is the presence of clinically significant portal hypertension as estimated by the hepatic venous pressure gradient (Ripoll 2007). In the decompensated phase, one can differentiate between patients who have a sole event as decompensating event (normally ascites or variceal bleeding) and those who develop more than one decompensating event (further decompensation). These patients are at risk of dying due to their liver disease (de Franchis et al. 2022).

Ascites is the most frequent complication, which marks the transition to the decompensated phase of the disease (D'Amico et al. 2014). The pathophysiology of the development of ascites follows the peripheral vasodilation and systemic inflammation hypothesis (Arroyo et al. 1996; Bernardi et al. 2015). In portal hypertension, patients have a marked splanchnic vasodilation, which leads to activation of vasoactive mechanisms such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system and the non-osmotic release of antidiuretic hormone. This leads to sodium retention in the nephron (mainly due to the activation of the RAAS). Together with the sodium, patients retain water, which ultimately leads to the accumulation of fluid in the abdomen. The diagnosis of ascites is established by clinical examination and ultrasound. Other common causes of ascites such as malignancy should be ruled out. Measurement of the serum ascites-albumin gradient (> 1.1 g/dL) allows the diagnosis of a portal hypertension associated ascites with an almost 97 % diagnostic accuracy (Runyon et al. 1992). Initially, the treatment of ascites includes administration of aldosterone antagonists with loop diuretics as well as the recommendation to a low salt diet (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018). As the disease progresses or in the context of acute events such as spontaneous bacterial peritonitis (SBP), ascites can accumulate and may require large volume paracentesis for symptomatic treatment. If the liver disease continues its progression, ascites control can become increasing challenging requiring increasing doses of diuretics or due to the development of complications secondary to the administration of diuretics such as renal failure or electrolyte disturbances (namely potassium and sodium). In this situation, the ascites is considered refractory and repeat large volume paracentesis with albumin reposition are needed. Refractory ascites is considered as further decompensation (de Franchis et al. 2021) and is associated with even a greater reduction of life expectancy (D'Amico et al. 2014). Refractory ascites is defined by the IAC (International Ascites Club) as the presence of ascites which cannot be mobilized or early recurrence of which, despite intensive diuretic therapy and intensive diuretic treatment (Arroyo et al. 1996). Although large volume paracentesis remains the first line treatment of refractory ascites, an alternative to repeat large volume paracentesis is the use of a transjugular intrahepatic portosystemic shunt (see further description in Ch. 3 and 8.6), which leads to an improvement in control of ascites and possibly a reduction in mortality (European Association for the Study of the Liver. Electronic address and European Association for the

Study of the 2018). Besides refractory ascites, there are other ascites-associated complications which can mark the transition to further decompensation such as SBP, dilutional hyponatremia or hepatorenal syndrome (HRS) (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018; de Franchis et al. 2021).

Hepatorenal syndrome refers to a “functional” renal dysfunction that occurs in patients with cirrhosis and ascites due to reduced renal perfusion secondary to hemodynamic alterations in the arterial circulation and activation of endogenous vasoactive system (Angeli et al. 2019). Traditionally (Arroyo et al. 1996; Salerno, Gerbes, et al. 2007), one distinguished between hepatorenal syndrome type 1, which was a rapidly progressive renal failure (increase of creatinine to greater than 2.5 mg/dL within two weeks) or hepatorenal syndrome type 2, which has a less rapid course, with a progressive increase of creatinine to greater than 1.5 mg/dL. Typically, hepatorenal syndrome type 1 takes place in the context of an acute event, whereas hepatorenal syndrome type 2 takes place in end-stage refractory ascites.

In 2015, the International Ascites Club (IAC) adopted a new classification of renal dysfunction in cirrhosis (Angeli, Gines, et al. 2015). This was motivated due to the fact that increasing evidence was available suggesting that serum creatinine could underestimate the real renal function in cirrhosis due to muscle wasting, increased tubular secretion of creatinine, increased volume of distribution which may dilute creatinine and interference with bilirubin. Furthermore, the use of thresholds, do not allow the flexibility that is required in order to confront a dynamic situation like hepatorenal syndrome type 1. For these reasons, the ICA proposed adopting the criteria proposed by The Kidney Disease: Improving Global Out-comes (KDIGO) guidelines, which define AKI as any of the following: 1) increase in sCr by ≥ 0.3 mg/dl (≥ 26.5 µmol/L) within 48 h; or 2) increase in sCr to ≥ 1.5x baseline, which is known or presumed to have occurred within the prior 7 days; or 3) urine volume < 0.5 ml/kg/h for 6 h. In the specific context of cirrhosis, the ICA proposed a modification of the KDIGO criteria by using only the first three criteria given the fact that urine output in cirrhosis can frequently not properly reflect the renal function as patients with cirrhosis are frequently oliguric due to avid sodium retention or have a falsely high urine output due to the use of diuretics. Furthermore, ICA proposed that if a baseline value within the previous 7 days is not available, a serum creatinine within the last 3 months before admission can be used.

According to the relative increase of creatinine, one can differentiate different AKI stages (See Table 1: AKI stages). Noticeably, one can have AKI despite the fact that the renal function is still within the given normal range. Inside AKI Stage I, one could distinguish between those who achieved a peak over sCr ≥ 1.5 mg/dL (Stage Ib) and those who achieved a peak below this threshold (Stage Ia), the latter of which may have a similar survival as those without AKI and in whom the AKI is more frequently reversible (Piano et al. 2013; Fagundes et al. 2013).

Table 1: AKI stages

AKI Stage	**Definition**
AKI Stage 1	increase in sCr ≥ 0.3 mg/dL (26.5 µmol/L) within 48h or an increase in sCr ≥ 1.5-fold to 2-fold from baseline[6]
AKI Stage 2	increase in sCr > 2-fold to 3-fold from baseline
AKI Stage 3	increase of sCr > 3-fold from baseline or sCr ≥ 4.0 mg/dL (353.6 µmol/L) with an increase ≥ 0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy

[6] Baseline means here the time before development of AKI

Acute kidney injury (AKI) occurs in approximately 20 % of hospitalized patients with cirrhosis (Belcher et al. 2013; Angeli, Gines, et al. 2015) and has been associated to mortality in patients with cirrhosis who have been hospitalized in regular wards (Belcher et al. 2013; Piano et al. 2013; Fagundes et al. 2013; Tsien, Rabie, and Wong 2013; Wong et al. 2013; de Carvalho et al. 2012; Angeli, Rodriguez, et al. 2015). Approximately 2/3 of acute kidney injury are due to renal hypoperfusion, which in turn can be divided into prerenal AKI (responsive to the administration of volume overload) or hepatorenal AKI (HRS-AKI) (unresponsive to the administration of volume overload (Belcher et al. 2013). Hepatorenal syndrome (HRS) type 1 (now included in hepatorenal AKI) has a high mortality of almost 100 % when left untreated (Gines et al. 1993) and is frequently part of multiorgan failure (acute on chronic liver failure). Among the etiologies of AKI in cirrhosis, hepatorenal AKI has the worst prognosis (Martin-Llahi et al. 2011).

The standard of care for the treatment of HRS is based on the use of terlipressin and albumin, which leads to an improvement in renal function (Martin-Llahi et al. 2008; Sanyal et al. 2008; Boyer et al. 2016; Wong et al. 2021) and a reduction in short-term mortality (Facciorusso et al. 2017; Allegretti et al. 2017), especially in those who have HRS reversal (Sanyal et al. 2008; Boyer et al. 2016). Despite the response to treatment, patients remain at risk for new episodes of HRS-AKI and death, so that liver transplantation should be considered in these patients (Angeli and Gines 2012). However, due to the limited organ availability and that many patients have contraindications to liver transplantation, this ideal possibility is feasible only in few patients (Brensing et al. 2000).

The transjugular intrahepatic portosystemic shunt (TIPS) is placed under radiological control and communicates the portal vein with a hepatic vein, leading to a reduction in portal pressure. Use of this shunt is part of the standard of care in patients with variceal bleeding and refractory ascites (Rossle and Gerbes 2010). The use of transjugular intrahepatic portosystemic shunt (TIPS) in the context of HRS is rationally plausible as it reverses portal hypertension, one of the main drivers of HRS, nevertheless this remains highly controversial (Rossle and Gerbes 2010). Indirect data suggests that it could lead to an improvement in renal hemodynamics and renal function (Jalan et al. 1997; Stadlbauer et al. 2008; Guevara et al. 1998; Busk et al. 2018). However, patients with HRS-AKI have frequently liver dysfunction and cardiac dysfunction that preclude TIPS placement ('EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis' 2010). Both the European Association for the Study of Liver Diseases (EASL) and American Association for the Study of Liver Diseases guidelines underline the lack of evidence to recommend TIPS placement in patients with HRS ('EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis' 2010; European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018; Biggins et al. 2021). The German guidelines suggest that TIPS placement in these patients may be considered (Gerbes et al. 2019).

The most recent guidelines for management of AKI in cirrhosis propose that in patients who have an initial AKI stage Ib or greater (increase of at least in 0.3 mg/dL or 1.5-2 fold baseline Creatinine to a final Creatinine greater than 1.5 mg/dL), initially causes of AKI should be evaluated (screening and treatment of infection, treatment of hypovolemia and removal of all nephrotoxic drugs, tense ascites) and treated respectively (Angeli, Gines, et al. 2015). If no cause is identified, diuretics (+/- beta-blockers) should be removed and volume expansion should be undertaken with albumin 1 gr per kg of body weight for at least 2 days. After this time period, the patient should be re-evaluated. If the AKI resolves, the patient should undergo close follow-up without further treatment. In the case that AKI remains, evaluation of the cause of AKI should be done including the evaluation of the HRS criteria. If other causes are ruled-out and therefore the patient fulfills the HRS criteria, treatment with vasoconstrictors and albumin

should be initiated. This proposal implies that therapy would be started earlier in the setting of HRS-AKI, before achieving the threshold for HRS Type 1. This approach has not yet been evaluated in clinical trials.

This study would be the first randomized controlled trial to fill this gap of knowledge. If the trial were to confirm our hypothesis, TIPS placement would have a clear role in clinical practice for the management of HRS-AKI since it could reduce mortality and morbidity and increase quality of life in patients with cirrhosis and HRS-AKI compared to the actual Standard of Care.

3 Medical Device

3.1 Background & rationale for use

The implantation of a transjugular intrahepatic portal systemic shunt (TIPS) is an interventional radiological procedure, which was developed in the 1980s. Initial attempts were hampered by the short-lived patency of the shunt (Gordon et al. 1987). However, technical improvements of the stent as well as of the procedure itself ameliorated the outcomes of the patients (Conn 1993). Although initially used for the treatment of variceal bleeding (Conn 1997; Rossle et al. 1997), an improvement of ascites was detected early on, so that randomized controlled trials were performed in this setting (Rossle 2013). The use of TIPS proved to be very effective in the management of complications of portal hypertension, although the initial positive effect was dampened by pseudointima hyperplasia in the stent, which led to stent dysfunction and recurrence of portal hypertension and its complications in the bare stents. In the first decade of the present century, a new stent coated with polytetrafluoroethylene was developed. This stent led to an improved stent patency and is now the standard of care (Bureau et al. 2004). In recent years, ePTFE covered stents in which the diameter can be controlled have been developed and associated to a decrease in complications after TIPS placement (Praktiknjo et al. 2021). Presently, the use of TIPS is approved for the management of complications of portal hypertension namely variceal bleeding and refractory ascites. The main complications associated to TIPS implantation are the development of hepatic encephalopathy, heart failure and worsening of the liver function (Boike et al. 2021; Rossle 2013).

In the setting of variceal bleeding, TIPS has been traditionally used in the context of an acute variceal bleeding refractory to endoscopical and pharmacological treatment or for patients who have a recurrent variceal bleeding despite an adequate secondary prophylaxis with endoscopic band ligation (EBL) and beta-blockers (de Franchis 2010). This approach had the disadvantage that by the time the refractoriness of the bleeding was determined or the recurrent bleeding occurred, patients were frequently too sick to benefit from a TIPS implantation. In 2010, a landmark paper was published which evaluated a modification of the timing of TIPS implantation in the context of variceal bleeding (Garcia-Pagan et al. 2010) . This study included high-risk patients with cirrhosis (Child-Pugh B with active bleeding or Child-Pugh C 10-13 points) and acute variceal bleeding. Patients were randomized within the first 72 hours after admission in the hospital for the bleeding episode to TIPS or standard of care. The primary end-point of the study was a composite outcome of failure to control acute bleeding or failure to prevent clinically significant variceal rebleeding within 1 year after enrollment. From the patients who were randomized to TIPS, 1/32 compared to 14/32 of the standard of care group reached this negative outcome. The patients who received TIPS had also a significantly higher survival rate at six weeks (97 % vs 67 %) and one year (86 % vs 61 %) (p=0.001). The incidence of hepatic encephalopathy was lower among patients who received TIPS (28 % vs 40 %) although this difference was not statistically significant. Since the publication of this trial, a number of trials have confirmed the beneficial effect of the early application of TIPS in the context of variceal bleeding and have been summarized in a meta-analysis (Zhou et al. 2021; Nicoara-Farcau et al. 2021).

As previously mentioned, although TIPS was initially applied in the context of variceal bleeding, it was noticed early on, that patients who had ascites before TIPS had no ascites thereafter. The use of TIPS for patients with refractory ascites was evaluated in a number of randomized controlled trials, which showed an improvement in ascites although no advantages in survival could be detected (Lebrec et al. 1996; Salerno et al. 2004; Rossle et al. 2000; Gines et al. 2002; Sanyal et al. 2003). In 2007, a meta-analysis with individual patient data included in 4 RCT was performed (Salerno, Camma, et al. 2007). In this analysis, an improvement in survival was observed, despite the fact that the trials were performed before the implementation of PTFE-covered stents, which have significantly lower dysfunction rate than the bare stents.

A more recent study evaluated the use of PTFE-covered stents at an earlier stage in the natural history of ascites (Bureau et al. 2017). In this study, 62 patients with ascites and at least 2 large volume paracenteses (but less than 6) were randomized to TIPS or standard of care. The primary end-point was one year survival. The patients who were randomized to TIPS had a significantly better survival rate than those who were randomized to standard of care (93 % vs 52 %, p =0.003), without an increase in the rate of hepatic encephalopathy. This study suggests that the benefits of TIPS are maintained when PTFE covered TIPS are used, and that patients with ascites benefit from a TIPS implantation earlier on in the disease.

In the setting of hepatorenal syndrome, the use of TIPS is highly controversial. On one hand it is well established that implantation of TIPS in patients with cirrhosis leads to beneficial effects for the kidney such as an improvement in renal blood flow (Jalan et al. 1997), an improvement in renal autoregulation in response to the perfusion pressure (Stadlbauer et al. 2008) , an improvement in the parameters of activation of vasoactive system (Guevara et al. 1998), an improvement in renal function (Brensing et al. 2000; Guevara et al. 1998; Busk et al. 2018) as well as a reduced incidence of HRS-AKI (Salerno, Camma, et al. 2007). On the other hand, patients with HRS-AKI (hepatorenal syndrome type 1) frequently have acute-on-chronic liver failure with increased bilirubin and hepatic encephalopathy, which may preclude TIPS implantation in these patients, due to high mortality (Brensing et al. 2000; Rossle and Gerbes 2010). Furthermore, cardiac dysfunction due to cirrhotic cardiomyopathy is proposed to have a central role in the development of HRS-AKI (Wong et al. 2011; Bernardi et al. 2015). TIPS leads to an increase in cardiac preload, so that its placement should be evaluated on an individual basis, especially in the presence of diastolic dysfunction (Rabie et al. 2009). The data that is available in the context of hepatorenal syndrome refers to the classical definition with type 1 and type 2. Most of the studies have focused on the use of TIPS in HRS type 2, which is per definition not HRS-AKI (Testino et al. 2003; Guevara et al. 1998; Gines et al. 2002; Ponzo et al. 2021). In the setting of HRS type 2, now named HRS-NAKI or HRS-CKD, the use of TIPS is effective and leads to an improvement of renal function (Testino et al. 2003; Guevara et al. 1998; Gines et al. 2002; Ponzo et al. 2021).

Two pilot studies have evaluated the use of TIPS in classical HRS type 1. One included only patients who had had a response to midodrine, octreotide and albumin. From the 14 patients with HRS type 1, only 10 had a response to treatment, of which 5 could receive TIPS. After 6-30 months of follow-up, all patients with TIPS were alive (1 with liver transplantation), while in the other group 3 had died (and 2 were alive with liver transplantation) (Wong, Pantea, and Sniderman 2004). A phase II study, evaluating TIPS in HRS (type 1 and 2) (n=41) had a subgroup of patients with HRS type 1 (n=21) (Brensing et al. 2000). Ten patients were excluded because of advanced liver failure, so 31 patients finally received TIPS (14 with HRS type 1). Survival improvement, both in the whole group and the subgroup with HRS type 1, was observed in the TIPS patients compared to those who were excluded from TIPS implantation, however the groups were by definition not comparable. A retrospective administrative data-

base analysis has shown that patients with HRS who received a TIPS had decreased in-hospital mortality [adjusted OR 0.43 (95 % CI 0.30-0.62] (Charilaou et al. 2020). Distinction between type 1 and type 2 HRS is not possible due to the study design.

3.2 Study Device

The medical device used within this study is the Gore® Viatorr® Controlled Expansion® Endoprosthesis produced by

W. L. GORE & ASSOCIATES, INC.
1505 North Fourth Street
Flagstaff, Arizona 86004, United States

who is represented within the European Union by

W. L. GORE & ASSOCIATES B.V.
Ringbaan Oost 152A
5013CE Tilburg, Netherlands

The manufacturer is not involved in any way in the clinical trial. The devices will be purchased by the sites and compensated by case payments. No special labelling will be applied. No special storage conditions apply ("avoid exposure to extreme temperatures and humidity. Store under ambient conditions"). Each site is required to keep a Medical Device Accounting Log to ensure traceability regarding use of a specific device.

This TIPS is comprised of an implantable endoprosthesis and percutaneous delivery catheter. Each device is for single-use only as the endoprosthesis will be permanently implanted after the procedure. One device per patient within the interventional group will be used. The inner diameter of the shunt can be chosen between 8, 10 and 12 mm by the treating physician.

The device is CE-marked (Notified Body No. 2797) and indicated for use in the treatment of portal hypertension and its complications such as: variceal bleeding refractory to, or intolerant of, conventional therapies, inaccessible varices, gastropathy, refractory ascites, and/or hepatic hydrothorax.

In the context of this study, the device will be used to treat another portal hypertension associated complication: hepatorenal syndrome AKI in patients with ascites. This indication is beyond the traditional indication established for TIPS use according the device's Instructions for Use (IFU). Nevertheless, the effect that is aimed for, namely a reduction in portal hypertension is the same as is in the traditional indications. The procedure for TIPS implantation will take place the same way as described within the IFU.

Contraindications and warnings for the use of the study device are adequately addressed in the inclusion and exclusion criteria. Possible adverse events related to the study device are listed in Ch. 9.3. The described precautions are covered by the study-specific requirements for study sites and personnel (refer also to Ch. 7.2). Please refer to the actual IFU for further information such as technical and functional characteristics of the device. Each site will receive the IFU with the Investigator Site File (ISF).

4 Risk-Benefit-Assessment

The treatment in the control group is the standard medical care in Europe. TIPS placement is an invasive procedure with inherent risks. The main complications associated to TIPS placement can be divided according to problems which are associated to the technique *per se* [i. e puncture of other structures (bile ducts, hepatic artery, extrahepatic); use of contrast medium in patients with AKI] and problems which are associated to the shunting that is aimed with the TIPS (such as hepatic encephalopathy, ischemic hepatitis, ACLF and heart failure). Nevertheless, it has become standard of care for different complications of cirrhosis including refractory

ascites. Furthermore, although direct evidence supporting this approach is lacking, TIPS placement is occasionally used in Germany in the context of HRS-AKI in cirrhosis. In the specific situation of HRS-AKI, there are two conditions which require special attention. Firstly, HRS-AKI is commonly part of an acute on chronic liver failure which is mainly associated with a worsening of liver function. Two recent studies have evaluated the use of TIPS, in this case early or pre-emptive TIPS, in ACLF in the context of variceal bleeding and have observed survival benefit for the patients who received TIPS, so that ACLF is not necessarily an absolute contraindication for TIPS placement in this context (Nicoara-Farcau et al. 2021; Trebicka et al. 2020). This study will provide further data on this point. The second specific safety issue in the context of HRS-AKI is that the presence of cirrhotic cardiomyopathy has, according to the present hypothesis (Wong et al. 2011; Bernardi et al. 2015), a central role in the development of hepatorenal syndrome type 1 (HRS-AKI). In order to overcome this issue, every patient will undergo a heart ultrasound to screen for any relevant cardiac disease. Patients with relevant cardiac disease will not be included in the study.

Due to the nature of the study and the TIPS placement and control, the specific risks for study participants is higher in the interventional than in the control group. For possible risks, please refer to Ch. 3 and 9.3.

The study specific risks regarding all study participants are very low compared to the overall risk of complications and death in patients with liver cirrhosis:

- study specific measures include only blood sampling as invasive measure; however, close routine laboratory examinations are necessary in patients with cirrhosis and AKI-HRS.
- the other study specific measures such as urine and stool sampling, abdominal ultrasound and questionnaires may be burdensome, but not invasive and not associated with any direct risk for the patient.

Also, the high number of on-site Follow-up Visits may be burdensome to some patients, but is necessary for safety reasons and to assess the disease course. Regular on-site visits (at least every 3 months) would be also scheduled for non-study patients.

Possible interactions of the study procedures with other medical treatments are either the same as in routine (for the control group with Standard of Care) or highly unlikely (TIPS group).

The following measures will be taken to assure a continuous risk-benefit-assessment:

- An independent Data Safety Monitoring Board (DSMB) will closely review safety data on a regular basis and will make recommendations regarding further conduct of the trial.
- The risk-benefit-assessment will be re-assessed by the principal coordinating investigator with every quarterly safety report to the BfArM.
- The frequent on-site follow-up-visits, especially within the first month after the procedure, guarantee early detection and countermeasures if adverse events occur

Despite the possible risk, the risk incurred by the individual participant is acceptable and ethically justifiable taking into account the potential benefit for patients with liver cirrhosis.

5 Study Rationale

5.1 Study Rationale and Hypothesis

TIPS implantation in patients with cirrhosis and portal hypertension leads to a reduction in portal hypertension, which in turn leads to a number of beneficial effects which ultimately lead to an improvement in renal function (Brensing et al. 2000; Guevara et al. 1998; Busk et al.

2018) such as increase in renal blood flow (Jalan et al. 1997), an improvement in renal autoregulation in response to the perfusion pressure (Stadlbauer et al. 2008) and an improvement in the parameters of activation of vasoactive system (Guevara et al. 1998). Traditionally the use of TIPS in patients with HRS has not been recommended due to the frequent association of HRS to ACLF and cirrhotic cardiomyopathy (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018; Biggins et al. 2021).

However, it is possible that an earlier TIPS implantation in patients with HRS-AKI stage 2 or 3 (instead of waiting that the patient fulfills the classical definition of HRS type 1) has a better outcome. Indeed, previous indirect data as well as small pilot studies have suggested that TIPS may be helpful in selected patients with HRS-AKI. Further information from an interventional study will help fill gaps of evidence-based knowledge in this area.

5.2 Objectives

5.2.1 Primary Objective

The primary objective of the study will be to evaluate the effect of TIPS implantation in patients with cirrhosis and ascites and hepatorenal syndrome associated acute kidney injury on 12-month liver transplant free survival.

5.2.2 Secondary Objectives

The secondary aims are directed at evaluating the effect of TIPS on renal function as well as transplant free survival at 3 and 12 months, as recommended in the recent position paper regarding end-points in studies in decompensated cirrhosis (Sola et al. 2021). Furthermore, the impact of TIPS implantation on the development of liver cirrhosis complications and the effect of TIPS on quality of life will be evaluated.

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoint is the 12-month liver transplant free survival. This endpoint has been recently recommended as the primary endpoint to be reported in trials in decompensated cirrhosis (Sola et al. 2021). This endpoint is a hard clinical endpoint, which is evidently patient-relevant. We hypothesize that the 12-month liver transplant free survival is higher in patients in the interventional group.

5.3.2 Secondary Endpoints

Secondary endpoints include:

1. 3-month liver transplant free survival
2. Requirement of TIPS implantation or TIPS revision during follow-up. The accepted indications for TIPS implantation/revision are
    a. Pre-emptive TIPS for variceal bleeding in patients with Child-Pugh C cirrhosis (≤13 points) or Child-Pugh B cirrhosis with active bleeding at endoscopy
    b. Recurrence of variceal bleeding in Child-Pugh A patients or Child-Pugh B patients without active bleeding at endoscopy despite adequate secondary prophylaxis with beta-blockers and endoscopic band ligation
    c. Refractory ascites as previously defined (see above)[7]
    d. Recurrent ascites as previously defined (see above)**Fehler! Textmarke nicht definiert.**
    e. Additionally, TIPS revision can be undertaken if there is a clinical suspicion of TIPS dysfunction

[7] this diagnosis can only be established if the patient is in a stable situation without complications such as bleeding and infection; diagnosis should be discussed with PCI on a case by case basis

3. Development of cirrhosis associated complications (further decompensation) during follow-up: overt hepatic encephalopathy, refractory or recurrent ascites, dilutional hyponatremia, new AKI-HRS, variceal bleeding
4. Reversal of HRS-AKI at 3 and 12 months (vs baseline), defined as return of serum creatinine level within 0.3 mg/dl (26 µmol/L) of baseline value.
5. Partial response to treatment at 3 and 12 months (vs baseline), defined as reduction of at least one AKI stage with decrease of serum creatinine to ≥ 0.3 mg/dl (26 µmol/L) above the baseline value.
6. In-hospital, 28-day and 90-day survival.
7. Length of in-hospital-stay
8. Relative changes in HrQoL (as measured by SF36 and CLDQ) at 3 and 12 months (vs. baseline)
9. Need for renal replacement therapy
10. Recurrence of HRS-AKI after treatment at 3 and 12 months
11. Development of acute-on-chronic liver failure during follow-up.
12. Impact of the presence of intrinsic nephropathy as assessed by cystatin C and UnGAL on outcomes
13. Association of pathophysiological mechanisms of cirrhosis with outcomes (in further studies)

Safety assessment / Secondary endpoint regarding safety:

14. The incidence of adverse events in the TIPS patients compared to standard of care (with specific focus on ischemic hepatitis, ACLF and heart failure)

5.3.3 **Choice of endpoints and time points for data collection**

The primary endpoint and secondary endpoints 1-11 as well as the safety assessment are directly related to the study aims. Most chosen variables are either hard clinical endpoints (such as survival and need for renal replacement therapy) or endpoints which can be clearly measured by given scores and definitions (e.g. reversal or recurrence of HRS-AKI; please see Ch. 14). Assessment of underlying laboratory values will be done by local laboratories which are subject to regular quality controls (Ch. 11.1). Changes in Quality of Life (assessed by questionnaires) are inevitably purely subjective but due to the use of standardized questionnaires a valid and meaningful endpoint.
The endpoints for exploratory analyses (such as analysis of cystatin C and UnGAL) are not directly related to the study aims but may provide additional information on future treatment of patients with cirrhosis and HRS-AKI.
The time points for data collection cover both short-term and long-term events and are chosen carefully to make a qualified statement about the course of the disease and the effects of the treatment. Endpoints such as Questionnaires are only collected at certain time points, whereas others need a continuous monitoring of the study participant for assessing the endpoint-relevant event (e.g. recurrence of HRS-AKI).

6 Study Design

6.1 General

This study is a prospective, 1:1-randomized, open, multicenter interventional trial. The control group will be a parallel group, which is managed according to the standard of care.

Due to the TIPS placement in the intervention group, no blinding is possible. Potential cross-overs are taken into account (please refer to Ch. 12.3).

6.2 Study Population

Eligible for the study are patients with cirrhosis and ascites and confirmed HRS-AKI. Only patients able to give informed consent themselves will be included, no especially vulnerable persons will be included or patients who are directly dependent on the investigator.

6.3 Randomization

Patients will be randomized in a 1:1 ratio to the TIPS or the SOC group. The randomization will be stratified according to AKI stage (II or III) and sites to adjust for site effects and potential effects caused by the severity of the underlying disease. For treatment with terlipressin, it is known that the response rate decreases with higher creatinine values at the start of treatment. Randomization of a patient will be done via an online tool of ZKS Jena (PaRANDies) to ensure that group assignment is unbiased and concealed from patients and investigator staff. A separate detailed description of the procedure will be provided by ZKS Jena.

6.4 Feasibility of Recruitment

It is intended to include 124 patients at approximately 10-15 sites in Germany within 24 months (corresponding to less than 1 patient/month/site). There is no limit to the number of subjects randomized at any individual study site. Sample size calculation is described in Ch. 12.1.

6.5 Time Schedule

The estimated study duration is approx. 50 months. All enrolled and randomized subjects will be followed through 12 months. The enrollment period is expected to take 24 months. Enrolment will be continuously monitored during the recruitment phase to allow timely countermeasures in case of lower recruitment rate as expected.

After the baseline visit, 13 follow-up on-site visits will be performed (see Ch. 1.4 and 8.7).

All study assessments are listed in Ch. 8.8.

Start of recruitment is planned for Q3/2022, Last Patient In is planned for Q3/2024. Last Patient Out (= end of study) with completed 12-months-Follow-up is planned for Q3/2025.

7 Participation

7.1 Study subjects

7.1.1 Inclusion Criteria

1) Patients with cirrhosis confirmed by histology or liver stiffness or with unequivocal signs in ultrasound, endoscopy and/or blood tests
2) Clinically evident ascites due to portal hypertension (SAAG > 1.1 g/dL) *Serum-ascites-albumin-gradient in case of ascites. The presence of hepatic hydrothorax is considered as an ascites equivalent. In this case instead of SAAG, the serum-pleural effusion-albumin-gradient > 1.1g/dL
3) HRS-AKI stages 2 or 3[8]
4) Planned vasoactive treatment for the management of HRS, as defined by the administration of terlipressin + albumin
5) Age: ≥ 18 to ≤ 75 years old at the time of consent

[8] HRS-AKI stage 2 and 3 are patients who have an at least two-fold increase in serum creatinine within 7 days before baseline in whom other causes of AKI have been ruled out (see exclusion criteria). If a baseline value within the previous 7 days is not available, a serum creatinine within the last 3 months (in a stable situation) before admission can be used.

6) ECOG < 4 prior to hospital admission
7) Subject has been informed of the nature of the study, is willing to comply with all required follow-up evaluations within the defined follow-up visit windows and has signed an Ethics Committee (EC) approved consent form.
8) Female subjects of childbearing potential have a negative pregnancy test ≤ 7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation. Female subjects will be exempted from this requirement in case they are sterile, infertile, or have been post-menopausal for at least 12 months (no menses). A contraceptive method with a pearl index below 1 % is assumed to be effective.

7.1.2 Exclusion Criteria

1) Patients with signs of intrinsic renal disease as defined by proteinuria (>500 mg per day), microhematuria (>50 RBC per high power field) or signs of chronic renal disease on ultrasound.
2) Recent or current use of nephrotoxic drugs (NSAIDS, Aminoglycosides or iodinated contrast medium) in the previous 72 hours
3) Improvement of renal function after 2 days of diuretic removal and plasma volume expansion with albumin 1 gr/kg
4) Uncontrolled shock
5) Patients with uncontrolled infection (defined by a 20% increase in inflammatory parameters (CRP, leucocytes or insufficient decrease of PMN in ascitic fluid < 25% from baseline in the case of a SBP) despite 48 hours of antibiotic treatment.
6) Patients with cardiac cirrhosis as defined by the development of cirrhosis in a patient with chronic heart failure due to a primary cardiac disease (ischemic cardiomyopathy, hypertensive cardiomyopathy, etc.)
7) Patients with contraindications to TIPS placement (Bilirubin > 5 mg/dL, recurrent hepatic encephalopathy)
8) Patients with cavernous portal vein thrombosis, splenic vein thrombosis or mesenteric vein thrombosis
9) Patients with clinically significant cardiac disease (NYHA ≥ II)
10) Patients with diastolic dysfunction grade 3.
11) Patients with a reduced systolic function with an ejection fraction ≤ 50 %.
12) Patients with an acute variceal bleeding at the time of screening who have indication for pre-emptive TIPS and/or terlipressin.
13) Patients with refractory ascites as defined by the International Ascites Club (less than 800 gr weight loss over 4 days in patients on low salt diet and high dose diuretics (spironolactone 400 mg /day and furosemide * 160 mg /day), or lower dose of diuretics with complications secondary to the use of diuretics such as hyponatremia, renal failure, hepatic encephalopathy. *equivalent dose of torasemide 40 mg/day
14) Patients with hepatocellular carcinoma outside of the Milan criteria (1 lesion maximum of 5 cm diameter or 3 lesions with a maximum of 3 cm of diameter)
15) Patients with hepatocellular carcinoma within the Milan criteria in whom the tumor is located in the puncture tract.
16) Patients with benign liver tumors (except regenerative nodules) which are located in the puncture tract
17) Patients with other comorbidities that lead to an estimated life expectancy under 1 year.
18) The subject is currently enrolled in another investigational device or drug trial.
19) Patients with pregnancy or lactation

7.1.3 Representativeness of the study population

The study population represents the overall population in this indication very well. The chosen inclusion and exclusion criteria are necessary to secure the diagnosis of HRS-AKI, to insure patient safety (e.g. contraindications for TIPS) and/or significance and validity of the collected data (e.g. ECOG ≤ 4 to ensure on-site-FU-visits, life expectancy > 1 year).

7.2 Participating sites

The clinical trial will be carried out multicentric in 10-15 trial sites in Germany.

The participating site must be equipped with the appropriate resources to fulfill the clinical study requirements as described in this CIP. The site selection includes but is not limited to the following criteria:

- The site is experienced in the management of patients with end-stage liver disease and performance of TIPS with PTFE-covered controlled expansion stents
- The site is experienced in the conduct of clinical trials regarding the treatment of end-stage liver diseases and experienced in the conduct of clinical trials with medicinal products
- The site is willing to participate in the trial and to undergo a monitoring and audit by sponsor and all relevant regulatory authorities. This includes the willingness to provide sponsor's representatives with an access to the hospital records, study files and subject files as they pertain to the study
- The site agrees to comply with the CIP and all regulatory requirements
- The site has a sufficient number of patients with cirrhosis with ascites and acute kidney injury.
- The site has the possibility to perform the described study assessments
- The leading investigator has to sign the Study Protocol Acceptance Form
- All investigators at the site have to sign the financial disclosure forms

Furthermore, TIPS placement is an intervention which should only be done in centers with a multidisciplinary team (including hepatologists, interventional radiologists (in the case the TIPS are placed by them), intensive care and general surgery with expertise in liver surgery (and ideally liver transplantation) and experience in the treatment of patients with decompensated cirrhosis. Indeed, the adjusted mortality rate after TIPS placement decreased in centers which placed more than 20 TIPS per year (Sarwar et al. 2018). The median number of TIPS placed in German centers with expertise in TIPS placement was 28/year (Steib et al. 2020). The procedure should be done by an interventional radiologist or a gastroenterologist/hepatologist who has experience in this procedure having performed at least 5 TIPS under supervision beforehand and at least 15 TIPS without supervision.

The leading investigator is responsible for choosing adequately trained and experienced study personnel, oversight, quality control at his/her site and confirms the availability of the necessary technical, personnel and time resources at his/her site on the site qualification form.

8 Study Conduct

8.1 Subject Screening and routine assessments for diagnosis of HRS-AKI

Potential subjects with cirrhosis and suspicion of HRS-AKI, aged ≥ 18 and ≤ 75 years will be screened for eligibility. All potential patients will be documented on the study-specific patient screening log. If inclusion is not possible, the reason should be given.

Patients potentially eligible for the study will be informed by an authorized and delegated investigator about the study and will be asked for his/her written consent. It is imperative that

written consent is obtained prior to any study-specific procedures. **Nevertheless, most of the screening visit procedures are done within routine clinical management and not exclusively related to study participation so they may be performed prior to informed written consent** (please see Visit Schedule Ch. 1.4). Particular attention should be paid to possible benefits and risks, possible side effects, voluntary participation and to the right of revocation without giving any reason. Patients should be given enough time for their decision (see Ch. 8.2.1).

Standard of care treatment for AKI will be started as recommended (Angeli, Gines, et al. 2015), namely diuretics will be paused and albumin will be given at 1 gr/kg per day (up to to a maximum of 100 gr per day) over two days. During this time period and prior to the inclusion in the study the patients will undergo anamnesis and physical examination, blood tests to evaluate the severity of the liver disease, the degree of renal function impairment and its possible consequences and to evaluate possible causes of renal function impairment. A 24-hour urine sample will be obtained as part of the routine evaluation of causes of renal function impairment, specifically to rule out intrinsic renal disease. Exhaustive evaluation of possible infections will be done including diagnostic paracentesis with evaluation of the PMN and fluid culture, urine culture and chest X-ray. A heart ultrasound will be performed to rule out cardiac causes of AKI. The administration of albumin and the above-mentioned examinations are required to rule out other entities that may be the cause of AKI including prerenal AKI. Lack of response to volume overload is defined as improvement of serum creatinine < 25 % from peak value and is required for the diagnosis of HRS-AKI. The patient can be checked for the other inclusion and exclusion criteria during this time. The investigator will review all the inclusion/exclusion criteria and will decide about eligibility of the patient for the study. Verification of inclusion/exclusion criteria will be documented. Once the diagnosis of HRS-AKI is established, and all inclusion criteria and none of the exclusion criteria are fulfilled, informed consent for participation in the study will be obtained.

8.2 Informed Consent

8.2.1 Obtaining informed consent

The subject's participation is voluntary. Only adult subjects capable of giving informed consent are included. It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study after adequate face-to-face explanation of the aims, methods, objectives and potential risks of the study (see Ch. 4, 9.3 and 9.5). The investigator must advise male patients to inform their female partner of childbearing potential about safe contraceptive measures. The informed consent has to be signed prior to any study-related assessment or procedure. All subjects will be informed of the aims, nature and scope of the study, the possible adverse events, the anticipated benefits of the treatment, the procedures and possible hazards to which he/she will be exposed. The subjects also will be informed about their rights and duties as study participant and the (scientific) processing of the captured data. All subjects have to be informed verbally and in writing by a study investigator. A patient information sheet in comprehensible/non-technical language will be handed out and the subject will have enough time to decide to participate in the study as well as for clarification of questions by a study investigator. The patient gives consent to the participation in the diagnostic and therapeutic procedures of the study as well as in the processing and storage of data. This includes consent to inspections where records may be reviewed by authorized individuals (e.g. Monitor, Auditor) of the sponsor or surveillance authorities. If the subject does not consent to the collection, processing and storage of his/her data, inclusion in the study is not possible. Before informed consent is obtained, the investigator has to provide the patient sufficient time and opportunity to inquire about details of the study and to decide whether or not to participate

in the study. All questions about the study have to be answered to the satisfaction of the patient. The patient´s written consent must be obtained before any study-specific activities. Therefore, the informed consent form must be dated and signed in duplicate by the subject and the investigator conducting the informed consent conversation. Only physicians who are authorized and delegated by the local PI may inform the patients and obtain the consent for the study. The signed original is archived by the investigator and a copy must be provided to the subject together with the patient insurance conditions. Provision of consent will be confirmed in the patient file by the investigator. It must be clear to study subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment. No special incentive for study participation exists, only reasonable reimbursement of the travel expenses to the on-site FU visits will be provided.

If the patient is eligible after careful consideration of all inclusion and exclusion criteria and informed consent is obtained, he or she can be randomized in the clinical study (group assignment).

In case that changes during the course of the study are necessary which affect the safety of the study participants or the study conduct for the study participants, a new patient informed consent form will be provided and the participants ask to re-consent. As it may be possible during the course of the study that study participants lose their ability to give informed consent by themselves due to their age or diseases, the sponsor will provide also an informed consent form for their legal representative (not applicable for first consent for study inclusion!).

8.2.2 Withdrawing informed consent

Study participants can withdraw their declaration of consent at any time and without giving reasons and thus terminate their participation in the study. In case of withdrawal of the consent, the patient's study participation is terminated, thus, no further study or follow-up visits will be conducted. The end of the study and the reasons (if known) must be documented. The decision to withdraw consent from the study treatment must be without any disadvantage for the patient. A final routine examination should be performed. Further treatment and follow-up outside the study should be ensured (see also Ch. 8.11.2).

8.3 Baseline Visit

Randomization is seen as part of the baseline visit, in which the following evaluations have to be performed:

- Demography (Age, Sex, Weight, Height, Racial background)
- Relevant Medical History with special focus on the history of the cirrhosis (including etiology, previous clinical decompensation (variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, acute on chronic liver failure; based on actual standards/guidelines), previous therapies including beta-blockers, lactulose, rifaximin, endoscopic band ligation, alcohol consumption
- Previous serum creatinine in stable situation (before development of HRS-AKI; = baseline serum creatinine)
- Health-related Quality of Life Questionnaires
- Women of childbearing potential must have a negative pregnancy (serum and/or urine) test within 7 days prior to randomization in accordance with the institutional standard of care. Female subjects who are surgically sterile or post-menopausal or elder than 50 years are exempt from having a pregnancy test. As a chest X-ray is usually performed as per routine in the context of AKI to rule out pulmonary infection, the pregnancy test is also usually done within routine.

8.4 Randomization

Patients who have signed the informed consent form and are considered eligible according to inclusion and exclusion criteria by the investigator will be randomized to one of the two the study groups: TIPS placement or only standard of care (terlipressin and albumin). Randomization will be performed centrally via an internet-based automatic system at the ZKS Jena (see Ch. 6.3). Randomisation should be done as soon as the inclusion and exclusion criteria are checked independently to the changes in creatinine after initiation of terlipressin. AKI stage for stratification is the stage which has been determined with HRS-AKI diagnosis.

8.5 Standard Treatment of HRS-AKI / Control Group

Once the diagnosis of HRS-AKI is established, the standard of care will be administered according to actual clinical practice guidelines(European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018) following the judgement of the attending physician (see below).

To bridge the time gap until the TIPS placement (scheduling for radiological intervention; no longer than 72h), patients in the interventional group will also receive standard of care until TIPS is placed. After TIPS placement the medication is to be weaned and discontinued.

Terlipressin will be started in continuous perfusion (2-4 mg per day) and will be increased in a stepwise fashion every 2-3 days in the case of non-response of serum creatinine (decrease in serum creatinine < 25 % from peak value). The maximum dose of terlipressin is 12 mg/day. Albumin will be given at a dose between 20-40 mg per day and adjusted according to the volume status of the patient. Treatment will be maintained until achieving a full-response (defined by regression of serum creatinine to within 26.5 µmol/L from baseline value) or a maximum of 14 days. Special attention will be given to volume overload. This will include daily physical examination including pulmonary auscultation and if considered necessary by the managing physician chest X-ray or measurement of central venous pressure or inferior vena cava diameter on ultrasound. If clinical suspicion of mild volume overload albumin will be reduced, if clinical suspicion of severe volume overload albumin will be temporarily suspended. Veno-venous hemodialysis will be initiated according to the decision of the managing physician. It is recommended that patients who require veno-venous hemodialysis do not receive further treatment with terlipressin +/- albumin, although this will be decided by the attending physician. The patient will remain in the study for the intention to treat analysis regarding the main end-point.

8.6 TIPS Procedure / Interventional Group

8.6.1 General aspects

Placement of TIPS is an interventional radiological procedure. A central access over the right jugular vein is obtained. Through this central access, the (right) hepatic vein is catheterized and then a needle is introduced in the hepatic vein. Under fluoroscopic and sonographic guidance, the needle is introduced through the liver parenchyma to the (right) portal vein branch. Once in the portal vein, the puncture tract (between the hepatic vein and the portal vein) is dilated with a balloon and the stent-graft is placed.

TIPS leads to a long-term reduction in portal pressure. Portal hypertension has a central role in the development of HRS-AKI, indeed the standard treatment leads to a temporary reduction in portal pressure. It is possible that long term portal pressure reduction with TIPS is helpful in this condition.

Placement of a transjugular intrahepatic portosystemic shunt is a routine procedure in patients with portal hypertension associated complications, namely refractory variceal bleeding, recurrent variceal bleeding despite appropriate secondary prophylaxis and refractory ascites.

8.6.2 TIPS procedure

Before the procedure, an evaluation of the patient to confirm the indication and to evaluate possible contraindications should be performed. Although in the recent Baveno Consensus Conference, performance of a CT before TIPS is recommended for vascular mapping and evaluation of the presence of splanchnic vein thrombosis, due to the characteristics of the study population (presence of AKI and therefore an increased risk of contrast-medium associated AKI (Danziger et al. 2015)) in the present study, the decision to perform a CT will be done on a case-by-case basis by the attending physician.

For the procedure, one needs a high-resolution flat-panel detector X-ray C-arm with digital subtraction angiography. Vital sign monitoring should be performed including non-invasive blood pressure, heart frequency, ECG and peripheral oxygen saturation. Furthermore, possibility to invasively measure and record intravascular pressure should be available. Ultrasound is frequently used to facilitate vascular punctures including both jugular vein as well as portal vein (Steib et al. 2020). For the TIPS placement, angiographic catheters and guidewires are required for accessing the hepatic veins. A TIPS-needle is required to puncture the portal vein. An 8-10 mm controlled-expansion ePTFE covered stent-graft is required and different angioplasty balloons in order to dilate the stent-graft to achieve the aimed reduction in the portal pressure gradient. Portosystemic collaterals may be embolized especially if these lead to a steal phenomenon.

Ideally, the TIPS placement should be done through the right hepatic vein into the right branch of the portal vein, around two centimeters away from the portal trunk bifurcation. In liver transplant candidates (or patients in whom liver transplantation may become a possibility in the future), special care should be taken to avoid a too proximal stent-graft position (i.e. until vena cava inferior or right atrium) or too distal stent-graft position in the portal vein (i.e. too close to the confluens) which could hinder future vascular anastomosis.
The aim of the TIPS placement is to lead a reduction in portal pressure gradient. The portal pressure gradient is calculated by the difference in the pressure between the portal vein and the vena cava inferior. This requires the measurement of the pressure in these vessels before (once the portal vein is punctured) and after the stent-graft placement. The stent-graft should be expanded in order to achieve a sufficient reduction in pressure with special care to avoid an excessive reduction in pressure, which would lead to increase in shunting and increase in the incidence of post-TIPS hepatic encephalopathy. **Only ePTFE covered stent-grafts are permitted in the present study**. **Before TIPS placement**, measurement of the pressure in the **hepatic vein** (free hepatic venous pressure), **in the main portal vein and in the vena cava** at the juncture with the hepatic veins **and in the right atrium is mandatory**. **Immediately after TIPS placement**, measurement of the **pressure in the main portal vein and in the vena cava** at the juncture with the hepatic veins **and in the right atrium should be measured again. The portosystemic gradient is calculated as the difference between the pressure in the main portal vein and the vena cava** (de Franchis et al. 2021). The procedure should preferably be done in deep sedation. The **TIPS should be placed initially with an 8 mm diameter**. A second measurement of the portal pressure gradient should be done **after a maximum of 72 hours without deep sedation. Mild sedation with low dose midazolam is permitted if necessary, although not recommended**. In this procedure, **the pressure in the main portal vein and in the vena cava inferior** at the junction with the hepatic veins should be measured.

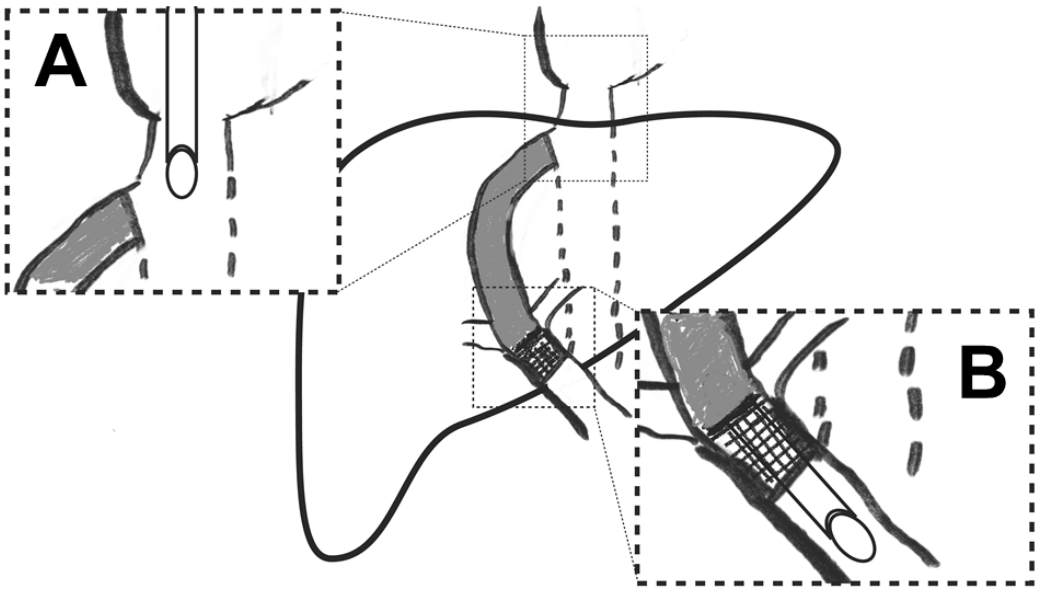


Figure 1: Localization of pressure measurements: A) measurement in the vena cava, B) measurement in the main portal vein. The TIPS is shown as the gray tube.

If **terlipressin is still being administered** by the second measurement, this **medication should be paused at least for 6 hours before the measurement**. The aim is to reduce the pressure to 8-10 mmHg, depending on the clinical characteristics of the patient. In the case of a very high (> 24 mmHg) or very low (< 15 mmHg) initial gradient, the aim would be to reduce the pressure from 25-50 % (de Franchis et al. 2021). All measurements of pressure must be registered in paper or digital format for at least 15 seconds. A routine TIPS requires approximately 15-20 minutes of X-ray fluoroscopy. Different measures (such as reducing the field of exposure, reducing the rate of fluoroscopy) are undertaken to reduce exposure. A second measurement of the portal pressure gradient requires on average approximately 2 minutes of X-ray fluoroscopy. During the procedure, use of contrast medium should be minimized and if possible CO_2 angiography should be used. Management of patients after TIPS should be done according to local standards, **anticoagulation or antiaggregation are not recommended taking into account the increased risk of these treatments in the context of AKI.**

8.7 Follow-up-Visits

All study subjects will be followed up for 12 months, until death or other defined end of study (EOS; see Ch. 8.11 for definitions for regular and premature EOS).

After the study treatment, the patient will continue his/her treatment on an in-hospital or outpatient basis according to the clinical situation. Initially daily visits are planned including anamnesis and physical examination and routine laboratory. Afterwards the visits will be done on a weekly basis the first month, on a monthly basis until month 3 and then every 3 months until the end of the participation in the study.

The study site has to make all efforts to schedule the visit in the appropriate timeframe. If the follow up cannot be completed within the time range, it has to be documented as a protocol deviation.

The follow-up visits have to be performed on-site and within the following time frames:

- day 1-5 (+/- 0 days)
- day 12 and 19 (+/-1 day)
- day 30 = 1 month FU and 2 MFU (-2/+ 7 days)
- 3, 6, 9 and 12 MFU (+/- 15 days)

As the FU visits within the first month after study inclusion are very close, no additional study visit for hospital discharge will be scheduled.

8.8 Study Assessments

8.8.1 Physical examination

At every study visit, a physical examination including evaluation of orientation (time, person, place) and presence of flapping tremor, evaluation of skin and mucosa, heart and lung auscultation, abdominal physical examination and presence of lower limb edema. Current alcohol consumption has to be elevated. Intake of low salt diet will be evaluated.

8.8.2 Laboratory Assessments

Blood tests are performed at every visit.

At every study visit, approx. 20 ml blood is taken from the study participants and analyzed in the local lab. Laboratory assessments include sodium, potassium, creatinine, ALAT, ASAT, GGT, AP, bilirubin, Albumin, INR, pH. These laboratory values are usually routinely taken for assessment of liver and kidney diseases. Wherever possible, data from routine blood tests are taken for the study to keep the burden for the patients as low as possible.

8.8.3 Abdominal ultrasound

Abdominal ultrasound will be performed at month 1, 3, 6, 9 and 12 to assess TIPS permeability. The ultrasound should be done with a machine with doppler ultrasound. In the ultrasound evaluation the following information should be recorded:

- Presence of ascites (none/subclinical/clinically evident)
- Suspicion of HCC
- Color Doppler ultrasound of the main portal vein, left branch of the portal vein, right branch of the portal vein (hepatofugal or hepatopetal flow) as well as the TIPS (normal/abnormal flow).
- Pulse wave Doppler measurement of the flow velocity in the main portal vein, at the beginning, middle and end of the TIPS.

8.8.4 Health-related Quality of Life Assessment

Health-related Quality of Life (HrQoL) will be assessed using the two questionnaires SF-36 and CLDQ at baseline and FU visits at 3 and 12 months.

8.8.4.1 SF-36

The Short Form 36 (SF-36) questionnaire is a globally established, validated and most widely used instrument for recording Patient Reporting Outcomes (PROs) in clinical trials and its validity has already been proven in numerous studies also in the context of chronic liver disease (Ware and Sherbourne 1992; McHorney, Ware, and Raczek 1993; Ware et al. 1999; Bonkovsky and Woolley 1999; Bryan et al. 1998). It is one of the most sensitive standardized status instruments and is often used in combination with disease-specific measurement instruments.

The SF-36 consists of 36 questions and is a general health questionnaire that provides a profile of two summary health components by assessing the patient's health status along 8 different dimensions:

- vitality - 4 questions
- physical functioning – 10 questions
- physical pain – 2 questions

- general health perception – 5 questions
- physical role function - 4 questions
- emotional role function - 3 questions
- social role function - 2 questions
- mental well-being – 5 questions

To evaluate the SF-36 questionnaire in version 1.0, all answers are first converted into given points using a scoring key. Then the average value of all questions of the respective health dimension (e.g. physical health) is calculated, resulting in eight average values for the eight dimensions. These describe the patient's state of health in the respective dimensions, which can then be evaluated using comparison tables (Hays, Sherbourne, and Mazel 1993; Ware 2000).

The possible score ranges from 0 to 100 points, with 0 points representing the greatest possible impairment of health, while 100 points indicate no health impairment ('36-Item Short Form Survey (SF-36) Scoring Instructions [Internet]. Rand.org. [cited 28 March 2021].' 2021).

Analysis of the components of the SF-36 reveals two distinct concepts: a physical dimension represented by the Physical Component Summary (PCS) and a psychological dimension represented by the Mental Component Summary (MCS) (Lins and Carvalho 2016).

Within this clinical trial, the Version 1.0 of the SF-36 is used, as there is no validated German version available for SF-36 Version 2.0.

8.8.4.2 CLDQ

The Chronic Liver Disease Questionnaire (CLDQ) is a disease-specific questionnaire and was developed and assessed as specific instrument for measuring health related quality of life in patients with chronic liver disease (Younossi et al. 1999). This questionnaire asks about symptoms related to their liver disease, how it affects their activities and how their mood has been. It has shown to better reflect the impairment of HRQoL that takes place as the liver disease progresses. The german translation of CLDQ has been validated in patients with liver disease in Germany (Hauser et al. 2004).

The questionnaire consists of 29 questions in 6 domains with 7 answer options for each question, ranging from the worst (1; “all the time”) to the best (7; “none of the time”) possible function.

The questions can be assigned to the following domains:

- Abdominal symptoms (AS): 3 questions (Items 1, 5, 17)
- Fatigue (FA): 5 questions (Items 2, 4, 8, 11, 13)
- Systemic symptoms (SS): 5 questions (Items 3, 6, 21, 23, 27)
- Activity (AC): 3 questions (Items 7, 9, 14)
- Emotional function (EF): 8 questions (Items 10, 12, 15, 16, 19, 20, 24, 26)
- Worry (WO): 5 questions (Items 18, 22, 25, 28, 29)

8.8.5 Renal replacement therapy

At every FU visit, it has to be assessed if renal replacement therapy (RRT) has been necessary. If yes, type and start date of RRT have to be documented.

In case of necessary RRT in patients in the control group, it is recommended to end the medication therapy with terlipressin and albumin, however this will be decided by the attending physician on a case-by-case basis.

8.8.6 Occurrence of HCC and need for liver transplantation

At every FU visit, it has to be assessed if the patient developed a hepatocellular carcinoma (HCC) and if a liver transplantation is necessary or has already been performed.

FU ends with liver transplant (both study arms), no further study related FU visits will be conducted thereafter. Patients will be followed up according to routine at the respective sites.

8.9 Indication for TIPS in the control group

One of the study end-points will be the development of a hard indication for TIPS placement (control group) or the need of TIPS revision (intervention group). TIPS placement and TIPS revision is indicated in the case of development of:

- massive bleeding requiring placement of an ELLA Danis stent or Sengstaken-Blakemore or Linton balloon (emergency TIPS)
- esophageal variceal bleeding (in patients with Child Pugh B 7-9 points and active bleeding at endoscopy or patients with Child Pugh C 10-13 points) (pre-emptive TIPS)
- recurrent esophageal bleeding despite adequate secondary prophylaxis with beta-blockers and endoscopic band ligation
- refractory ascites as defined by the IAC (see Ch. 14.4) (Arroyo et al. 1996)
- recurrent ascites as defined by the need of 3 large paracentesis within 3 months (in stable situation). Only paracentesis that take place in a stable situation, **namely without concurrent infection, without AKI, without bleeding, etc.** will be considered (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018).

If a patient randomized into the control group develops indication for TIPS (except emergency TIPS or pre-emptive TIPS) during Follow-up, the treating study physician should consult the Principal Coordinating Investigator to discuss the indication before TIPS implantation.

8.10 Collection of biosamples

Blood and urine and optional stool samples for the central laboratory will be obtained at baseline, 3, 6, 9 and 12 months. These will be obtained in order to evaluate in further research the pathophysiological mechanisms involved in the development of HRS-AKI such as the activation of vasoactive parameters (Renin, Aldosterone, Noradrenalin) and bacterial translocation (IL-6, Endocab, LBP). An initial planned exploratory subanalysis will be performed according to blood and urine markers of functional or organic renal impairment (Cystatin C and uNGAL). Stool samples will be optionally collected for future exploratory analysis regarding the influence of the gut microbiome on outcomes. Embedded future substudies for research on HRS will have their specific protocol and will obtain specific approval from the ethic committee separately.
The samples will be stored at the sites at -80ºC until end of the study and shipped on dry ice to the central laboratory. For further sample processing, please refer to the separate manual.

8.11 End of Participation

8.11.1 Regular end of study

The regular end of the study for the study participant is one of the following, whatever occurs first:

- 12 Month-FU
- Death
- Liver transplantation

After occurrence of EOS, no further FU visits are done. Once the patient finalizes the follow-up in the study, he/she will return to routine clinical follow-up in the outpatient clinic every 3-6 months depending on the clinical condition including screening ultrasound every 6 months when indicated.

Please note that with liver transplantation the medical device in the interventional group is explanted.

8.11.2 Premature end of study / discontinuation of study participation

Premature end of the study / discontinuation of study participation is defined as:

- Lost-to-Follow-up
- Withdrawal of informed consent (see. Ch. 8.2.2)
- Withdrawal at the investigator's or sponsor's discretion

A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include 3 attempts to make contact with the subject via telephone and if contact via telephone is not successful, a certified letter from the investigator must be sent to the subject's last known address. Should both telephone and mail efforts to contact the subject be unsuccessful, the subject's general practitioner should be contacted. All contact efforts to obtain follow-up information must be documented.

If a patient permanently discontinues and is unwilling or unable to attend regular study visits at the study site, the investigator and patient must determine which of the follow-up options the patient is able and willing to comply with. The patient will be approached to provide consent for further follow-up at the time of withdrawal. Options for follow-up of these patients are listed below, in descending order of preference:

1. Patient is unable or unwilling to attend this regular study visit, but will attend further study visits
2. Patient will be contacted by phone at the regular study visit intervals.
3. Patient allows his/her general practitioner (with a signed release of medical information) or a family relative to be contacted at the regular study visit intervals.
4. Patient will be contacted once at the end of the study.
5. No further contact.

For patients who withdraw consent for any kind of follow-up, the patient's vital status will be obtained at study end through applicable information sources according to local guidelines and as allowed by local regulations. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. This information might be relevant for analysis in case of AE as reason. If provided, the reason for withdrawal has to be recorded in the eCRF and in the patient's medical records.

The investigator may terminate the study participating for the patient in the case of lack of compliance or other circumstances, which make study-relevant follow-up impossible. The sponsor might also decide to withdraw a patient from study participation (reason has to be specified e.g. major protocol violation). If a patient decides to discontinue the study after randomization (control or interventional group) but before respective start of treatment patients will be considered as drop-outs.

8.12 End of the Clinical Trial

8.12.1 Regular End of the Trial

The regular end of the trial is defined as the date when the last patient has completed the FU visit after 12 months (Last Patient Out (LPO)).

The sponsor reports the completion of the trial to the relevant regulatory authority. The sponsor submits the final report to the regulatory authority within 12 months after completion or premature termination of the clinical trial. The sponsor will also submit the final report to the EC, if required.

8.12.2 Premature Termination, suspension of the trial, closure of sites

A premature discontinuation of a single study site or of the study as a whole must be documented adequately with reasons being stated and information must be conveyed according to national requirements (e.g., EC, CA and local regulatory authorities). The Sponsor/coordinating investigator, the Competent Authority (BfArM) and the Independent Ethics Committee have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single study site, although this should occur only after consultation between the involved parties. Possible reasons for termination of the study at a study site could be but are not limited to:

- Unsatisfactory enrolment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Unexpected accumulation of SAE/AE
- Major failure to adhere to the study protocol

In addition, the investigator might terminate the study at their site prematurely, e.g. for unforeseeable circumstances which preclude the continuation of the clinical study at the site or the investigator considers that the resources for continuation, e.g. personnel or time, are no longer available.

If the investigator terminates or suspends a trial site without prior agreement of the sponsor, the investigator will promptly inform the sponsor and the EC and will provide the sponsor and the EC with a detailed written explanation of the termination or suspension. Should a center be closed prematurely, all trial materials (except documentation that has to remain stored at center) must be returned to the sponsor.

The Sponsor, the authorities and the EC have the right to terminate this clinical study as a whole prematurely at any time for reasonable medical or administrative reasons. For example:

- Unexpected accumulation of SAE/AE
- Change of risk-benefit considerations
- The reason for premature termination of the entire study could be also:
- A new finding concerning significant superiority or inferiority in one of the treatment arms, with regard to the primary endpoint data
- Coordinating investigator’s decision after unacceptable risks and toxicities have occurred, upon recommendation of the Data Safety Monitoring Board (DSMB)
- The new scientific findings during the course of the study which either give the answer to the primary and secondary endpoints or indicate that the further continuation of the study is not meaningful any more.
- The study does not prove feasible any longer
- In case of contract termination by the financial sponsor
- If the DSMB raise concerns about the safety of the TIPS device in this indication/study population

Any premature termination or suspension of the trial must be discussed with the DSMB as appropriate.

If the trial is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the respective regulatory authority and the EC according to § 64 (2) MPDG within 15 days, and provide the reason(s) for the premature termination or suspension. If the trial is prematurely terminated or suspended for any reason, the investigators will promptly inform the enrolled patients in agreement with the sponsor and ensures their appropriate treatment and follow-up.

If the sponsor temporarily suspends or prematurely terminates the trial for safety reasons, the respective regulatory authority and EC have to be informed within 24 hours.

The sponsor submits the final report to the regulatory authority in charge within 12 months after completion or premature termination of the clinical trial. The sponsor will also submit the final report to the EC, if required.

9 Safety

9.1 Definitions

9.1.1 Adverse Events (AE)

According to **MDR** an 'adverse event' means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

According to **ISO 14155:2020(E),** an adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device and whether anticipated or unanticipated. This definition includes events related to the investigational medical device or the comparator and includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Added in **MDCG 2020-10/1** with following note:

a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

The disease or symptom that led to the necessary intervention should be documented as an AE (not the medical or surgical intervention).

Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the medical product are not considered adverse events after treatment unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A pre-existing concomitant disease is not considered as an AE. In the case of a worsening the concomitant disease has to be considered as AE. If the worsening comes to be serious it must be further reported as a SAE.

Interventions, to treat a pre-existing condition that were already planned before consenting to the clinical trial, have not to be documented as AEs.

Daily fluctuations in the clinical picture are not considered as AEs.

9.1.2 Adverse Events of Special Interest (AESI)

The adverse event of special interest (AESI) are

- ischemic hepatitis defined by a threefold increase in transaminases (ASAT/ALAT) compared to baseline value
- ACLF as defined by the CLIF criteria (Arroyo, Moreau, and Jalan 2020)
- heart failure defined by the development of lower limb edema (without significant ascites) and/or pulmonary edema
- hepatic encephalopathy as evaluated clinically and graded using the West-Haven criteria (Bajaj et al. 2011)
- development of PC (post contrast)-AKI as defined by an increase of serum creatinine PC-AKI and of ≥ 0.3 mg/dl, or of ≥ 1.5-1.9 times baseline (KDIGO definition of AKI) in the 48-72 h following CM administration (van der Molen et al. 2018).

9.1.3 Serious Adverse Events (SAE)

According to **MDR** Art. 2 (58), a serious adverse event' means any adverse event that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
    (i) life-threatening illness or injury,
    (ii) permanent impairment of a body structure or a body function,
    (iii) hospitalisation or prolongation of patient hospitalisation,
    (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    (v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

In accordance with **ISO 14155:2020 (E)**; 3.45 serious adverse event means an adverse event that led to any of the following

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1) life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death, a congenital abnormality or birth defect including physical or mental impairment

9.1.4 (Serious) Adverse Device Effects ((S)ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the used medical device. This also includes any event that is a result of a use error or from intentional abnormal use of the investigational medical device (in accordance with ISO 14155.2020(E)). A serious adverse device effect is an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event (MDCG 2020-10/1 and ISO 14155.2020(E)).

According to BfArM an adverse device effect is a (serious) adverse event that has a causal relationship with the investigation procedure or where such causal relationship is reasonably possible (Article 80(5) and (6) MDR).

9.1.5 Device Deficiencies

According to MDR Art. 2 and ISO 14155:2020 (E) ‘device deficiency’ means any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information and labelling supplied by the manufacturer. This definition includes device deficiencies related to the investigational medical device or the comparator. As the comparator in the Liver-HERO study is the standard medication, device deficiencies can only occur in with the TIPS device.

Special observation is required for any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred or circumstances had been less fortunate (MDR) Article 80(2).

9.1.6 Incidents

Independent from participating in clinical studies every user of a medical device has an obligation to report suspected serious incidents to the competent authority. In Germany these reporting obligation is regulated in MPAMIV §§ 2 and 3 additional to Article 2 (64) and (65) MDR:

Article 2 (64) MDR

‘incident’ means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect;

Article 2 (65) MDR

‘serious incident’ means any incident that directly or indirectly led, might have led or might lead to any of the following:

a. the death of a patient, user or other person,
b. the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
c. a serious public health threat;

This means that all those who professionally or commercially operate or use medical devices (also health professionals like physicians) are obliged to report suspected serious incidents. A suspected serious incident

is defined by the MPAMIV as an incident where a serious incident cannot be ruled out according to MDR 2017/745. For persons who use medical devices professionally or commercially, the notification must be made immediately to the BfArM as the competent higher federal authority.

9.1.7 Relatedness

Each AE will be assessed by investigator whether a causal relationship with the medical device or study procedure may be possible or not. Each SAE submitted by the trial centres, will also undergo a secondary assessment by an experienced medical specialist delegated by the sponsor with regard to the criteria "serious", "causal relationship" and "expectedness".

Definitions of **causal relationship to medical device** are as follows:

Not related: bears no relation to timing of device and is similar to symptoms or signs expected in the disease process

Possible: bears relation to timing of device and is similar to symptoms or signs expected in the disease process

Yes: clear relation to timing of device and is distinct from symptoms or signs expected in the disease process

Definitions of **causal relationship to study procedure (TIPS implantation and control angiography)** are as follows:

Not related: bears no relation to timing of TIPS implantation.

Possible: bears relation to timing of TIPS implantation

Yes: clear relation to timing of TIPS implantation independent from whether or not it requires re-intervention or disappears on its own

9.1.8 Intensity

The intensity of adverse events will be classified according to the following 3-point scale.

Mild: a clinical symptom or sign that is well/easily tolerated and usually requires no intervention

Moderate: clinical symptom or sign sufficient to interfere with normal/daily activity, intervention may be required

Severe: a clinical symptom or sign that results in severe disability, inability to work or inability to perform everyday activities = daily activities/work not possible, treatment or intervention usually required

9.2 Reporting

(S)AE and AESI recording and documentation start for all subjects with randomization and ends with the 12-month follow up visit or with the prematurely end of study for the subject (death, liver transplantation), whichever event occurs earlier.
All SAE that are still ongoing at the 12-month FU or other regular or prematurely end of the study for the subject should be followed up until they are resolved or the investigator confirms that no further improvement or deterioration is expected.

9.2.1 AE Reporting

Any AE (or AESI) must be documented in the eCRF as soon as possible by the investigator or study center staff. In addition to other information, it must also be documented in the eCRF whether it is an SAE as stated in the definition in chapter 9.1.3.

9.2.2 SAE Reporting to sponsor

The (principal) investigator reports to the sponsor of this study according to § 63 MPDG

1) Without delay
    a. every serious adverse event within the meaning of Art. 2 No. 58 MDR and
    b. every device deficiency within the meaning of Art. 2 No. 59 MDR which, in the absence of appropriate measures or intervention or under less favorable circumstances, could have led to serious adverse events.

According to § 62(2) MPDG, (principal) investigators ensure that the investigational product suspected of having caused a serious adverse event (SAEs) is not discarded before the assessment of the competent federal authority has been completed. This does not preclude them

from making the investigational product available to the manufacturer or sponsor for the purpose of the investigation.

In the event of a SAE (included AESI), the investigational site must report by fax (+49 (0) 3641 9 39 99 46) immediately (without undue delay) after knowledge of the event.

In order to transfer all significant information, the SAE Report Form (filed in the ISF) provided by ZKS Jena must be used. Every available follow-up information must be provided as soon as possible. Please refer to the Working Instructions filed in the ISF for further information.

9.2.3 Reporting to authorities by sponsor

Serious adverse events related to a CE marked device which is part of the investigation procedure are reportable per MDR Article 80(2) if there is a causal, (or reasonably possible) relationship to the device, the comparator or the investigation procedure. The reporting procedures described in the guide MDCG 2020-10/1 should then be followed in addition to the normal vigilance reporting procedures for CE marked devices.

The reporting and notification obligations of the sponsor in other clinical trials result from § 64 MPDG:

1) The sponsor reports immediately to the competent higher federal authority via the German medical product information and database system in accordance with Section 86
    a. any serious adverse event (SAEs) within the meaning of Art. 2 No. 58 MDR which has a causal connection with the investigational device, the comparator or the investigational procedure or for which a causal connection appears entirely possible,
    b. any product defect within the meaning of Art. 2 No. 59 MDR which could have led to serious adverse events (SAEs) in the absence of appropriate measures or intervention or under less favorable circumstances.
2) If the sponsor temporarily suspends another clinical trial (German “sonstige Klinische Prüfung”) or breaks off the clinical trial, he/she shall notify the competent ethics committee, the competent higher federal authority and the authority responsible for him/her as well as the authorities responsible for the trial sites via the German medical product information and database system according to § 86 within 15 days, stating the reasons. The notification pursuant to sentence 1 is made within 24 hours if the sponsor temporarily suspends or terminates the clinical trial for safety reasons (see also Ch. 8.12.2).

The sponsor reports SADEs to BfArM immediately by SADE-Form.

The sponsor reports all occurred SAEs quarterly via MDCG SAE report table to the German BfArM and to all sites. The ECs receive the MDCG SAE report table as requested.

Additionally, the sponsor sends with the quarterly report a cumulative SAE Assessment to BfArM and to the ECs as required.

9.2.4 Device complaints

The site must report each incident to the competent authority according to the MPAMIV.

Participating in the study does not release the physician from his/her obligation to report incidents according to the respective local regulations to the competent authority!

Incidents of any medical device with CE sign that have occurred in Germany irrespective of a clinical study have to be reported to the competent authority by the device user following the instructions on the homepage:

https://www.bfarm.de/EN/Service/Forms/medDev/mp-forms-startseite_en.html (future reports via DMIDS (formerly: DIMDI))

9.3 Risks associated with the Investigational Medical Device and Procedure

TIPS placement is an interventional procedure, which in experienced hands has low risk, but is not absent of all risk. The rate of major complications after TIPS implantation should remain under 5 % and the mortality rate under 1 %. The main complications associated to TIPS placement may be associated to a) the procedure itself such as puncture of other structures such as the biliary tract, the hepatic artery or an extrahepatic puncture. In order to avoid an inadequate position of the stent, injection of contrast medium should be performed before the placement of the stent-graft. Extrahepatic punctures can be minimized by real-time ultrasound guidance for the placement of the stent. Further complications may develop after TIPS placement due to the shunting of the blood from the splanchnic circulation directly into the systemic circulation namely heart failure and hepatic ischemia. In order to foresee complications and be able to react swiftly, blood test evaluation including transaminases, liver function (mainly bilirubin and INR) as well as blood cell count should be performed the day following the procedure. Due to the shunting, patients with TIPS may develop hepatic encephalopathy, which may be avoided with prophylaxis. In the case a hepatic encephalopathy develops, it will be treated according to the standard of care. A very infrequent complication is an infection of the stent-graft also known as “Endotipsitis”, which can ultimately require liver transplantation for its treatment. Prophylactic antibiotics may be considered depending on patient and local risk factors.

The following risks are associated with the study device and potential adverse events include, but are not limited to, the following (Bettinger et al. 2016; Billey et al. 2019).

- Allergic reaction (contrast medium, medications)
- Arrhythmias
- Cervical hematoma
- Puncture of the carotid artery
- Pneumothorax
- Extrahepatic puncture
- Liver hematoma
- Puncture of the hepatic artery or bile ducts
- Vascular thrombosis
- Vessel injury (e.g., dissection, perforation, rupture)
- Ischemic hepatitis
- Heart failure
- Hepatic encephalopathy
- Contrast-medium induced acute kidney injury
- Infections
- Death

There may be other potential adverse events that are unforeseen at this time.

The IFU of the investigational device gives explicit warning for patients with biliary obstruction, pneumonia, adult respiratory distress syndrome, pulmonary hypertension, non-cavernomatous complete obstruction of the portal vein, cholangitis, or bacteremia. For these patients the risk and possible side effects of a TIPS must be weighed against the potential benefit of this procedure. These patients are not included in the present clinical study.

9.4 Evidence in the Occurrence of Pregnancy during the Study Period

Due to the nature of the underlying disease and therapy, no pregnancies are expected. Women with decompensated liver cirrhosis usually cannot get pregnant due to lack of ovulation / amenorrhea. Terlipressin as standard of care must not be given to pregnant women due to its side effects. Nevertheless, the following precautions should be taken:

Appropriate precautions must be taken by women of childbearing potential. Patients (women of childbearing potential as well as men with the desire to have children) should use appropriate methods of contraception within three months after the index procedure. Reliable methods of contraception are described in the patient's information.

Pregnancy occurring during the clinical study, although not considered a serious adverse event, must be reported to the sponsor. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported.

9.5 Radiation protection

At the moment only limited data are available regarding the radiation exposure of the patient and the surgeon during the application of a TIPS. The German radiation protection office (Bundesamt für Strahlenschutz, BfS) also currently does not provide any reference values for this intervention. Miraglia et al. were able to show in a small collective that the mean dose area product is 235 ± 198 Gy cm^2 and the mean effective dose for the operator as 1.40 ± 2.68 µSv (Miraglia et al. 2016). In addition, this team and David et al. provided evidence for a significant reduction in radiation exposure through ultrasound-guided puncture of the portal vein system in contrast to a fluoroscopically guided approach (David et al. 2019; Miraglia et al. 2017).

The investigators are free in the choice of method they use for the TIPS application.

10 Data Management

10.1 List of responsibilities / Training

The list of responsibilities (Signature and Delegation Log) identifies all study site staff members involved in the clinical trial with their names, signatures and abbreviations, as well as their responsibilities and authority. This list must be filed in the ISF and in the TMF. All staff has to be trained sufficiently for the delegated responsibilities and re-trained when aspects of the study are changed. The training has to be recorded in writing (Training Log).

The principal Investigator at site has adequate experience in the field of the study specific indication and designates a deputy with comparable qualification before the start of the study. He/she has to lead and supervise his study team which consists of qualified persons in the field of the study specific indication. The principal investigator is also obliged to forward any study specific information (e.g. study protocol, product information) or updates of these documents to the study team. He/she is responsible for conducting the clinical study in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (current version) as well as with the International Council on Harmonization of Technical Requirements of Pharmaceuticals for Humans Use (ICH) especially Guideline for Good Clinical Practice (ICH, E6,) and the relevant national laws and applicable regulatory requirements. The principal investigator is responsible for the treatment of the patients, for the SAE declaration to the sponsor and the CRF documentation.

10.2 Screening

For all patients potentially eligible to participate in the clinical trial, inclusion and exclusion criteria will be reviewed. Documentation of these patients is required in a “screening and enrolment log”. All eligible patients must be documented, regardless of the later participation in the clinical trial (pseudonymized data). Reasons for non-participation of an eligible patient must be indicated.

10.3 Patient identification list

A confidential log of the names of all study patients with the identification code assigned to each patient at the time of enrolment in the clinical study. With this list, the identity of each patient can be revealed (key list for pseudonymization). The list must be kept confidential and must be maintained and stored exclusively at the study site in the investigator site file (ISF). It must not be copied or otherwise be passed on; no duplicates of this list may be made. The personal data collected and generated in the course of the study are processed and stored at the sponsor site solely based on the patient identification number in order to maintain the pseudonymization. However, sponsor representatives, clinical research associates (CRA), auditors and representatives of competent authorities (CA) must be allowed to inspect the list on request.

10.4 Medical Device Accounting Log

The sites have to keep a record over the used medical product under investigation that traceability in case of recall from the market is possible. Other regulatory recording requirements may apply which is in the site’s responsibility.

10.5 Investigator Site File (ISF)

The ISF will keep the documents required for the clinical trial, and will provide an overview on the clinical trial at the respective trial center. The ISF contains the essential documents, such as the trial protocol, patient information and consent form, approval of the competent authorities, approval of the responsible ethics committee (s), notification to the competent state authorities, investigators' CVs, list of responsibilities, trial-related correspondence, and other relevant documents.

As part of the monitoring process, the ISF will be checked to ensure it is up-to-date and complete in accordance with the regulations.

The investigator will be provided with an investigator site file (ISF) containing all necessary essential and relevant study documents for the initiation of the study at his/her site. The essential documents include a list on which the investigator will enter all appropriately qualified persons to whom he/she has delegated important study-related tasks. The investigator, or an individual who is designated by the investigator, will be responsible for the maintenance and completeness of the study documents during the clinical study. At the request of the CRA, auditor, EC or CA(s), the investigator shall make available all the requested study-related records for direct access. This file and associated study-related documents must be safely archived after termination of the study for at least 10 years. The investigator is responsible to ensure that the patient identification list is stored for at least 15 years beyond the end of the clinical study. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. The investigator will be responsible for the storage.

10.6 Case Report Form (CRF)

Data capture takes place via a web application on the servers of Center for Clinical Studies at Jena University Hospital with a study management software that meets all regulatory requirements (GCP, 21CFRPart11). Data is recorded via an encrypted data link (HTTPS) by use of data entry masks. In order to ensure a pseudonymized data analysis, a unique patient identification number is assigned to each patient.

The CRF consists of individual sections, including inclusion and randomization, visits during the study, AE/SAE, end of intervention and termination of the clinical trial. All appropriate sections of the eCRFs must be completed. For each patient, an own eCRF will be completed. It is the investigators' responsibility to ensure that all data collected during the trial are entered correctly and completely into the database specifically created for this trial. The eCRFs will be reviewed and signed by the site’s Principal Investigator or his designees.

Data management is done by using a study management software, which enables checking of data plausibility by range-, validity- and consistency-checks during and after data entry. Missing or obviously erroneous values produce query messages. Any modification of the data is documented in the database by an audit trail. The study database will also be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. Corrections in the eCRF may only be made by authorized persons or by the investigator-in-charge/head of unit/medical director of the trial group and must be justified.

A paper based CRF as a "copy" is provided to the trial sites as part of the ISF.

The data collection serves a scientific purpose.

The electronic data will be backed up regularly. The data storage is located in a locked room that should only be accessible to system administrators.

Data to be collected on screening failures and dropouts: Screening failures are defined as patients who signed an ICF but failed to be randomized in the study for any reason. These patients are to be documented on the subject screening log (see Ch. 10.2), no further documentation in the eCRF is required. Drop outs as defined according to Ch. 12.2.1 have to be documented on the subject screening log as well as on the patient identification log (see Ch. 10.3), for further data see notes for documentation (separate document in ISF).

10.7 Source Documents

The investigator is responsible for the filing of the relevant medical documentation for each study subject in the patient’s/subject’s medical records. The investigator has to keep a written or electronic subject/patient file for every subject participating in the clinical study. In this file study participation, date and process of informed consent, study visit dates, examinations and clinical findings, relevant medical history and relevant concomitant treatment, observed AEs and reason for withdrawal from the study if applicable of each study patient will be recorded. It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file. Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. The medical evaluation of such records should be documented as necessary.

For the current study, documents considered to be source data include original documents, data and records such as (but are not limited to):

- Subject’s record (subject’s medical file).
- Signed Patient Informed Consent Form
- Evaluation check lists

- Device printouts
- Any other records maintained to conduct and evaluate the clinical study
- Documentation of results and findings

10.8 Data handling

The data collection serves a scientific purpose. The data is generated in the participating study centers and collected via a web application on the servers of the organization responsible for data management. The software meets the regulatory requirements. The data is entered via an encrypted data connection (HTTPS) in input masks using a web browser.

The accuracy of the data is verified by validity and consistency checks. Implausible or missing data are requested from the study center. Every change to the data, e.g. by recording answered questions, is documented in the database via an automatic change tracking (audit trail). A hierarchical, role-based access concept prevents unauthorized access to the data.

The electronic data will be backed up regularly. The data storage is located in a locked room that should only be accessible to system administrators.

10.9 Data protection

Records and documents related to the clinical trial e.g., patient identification list, informed consent forms, correspondence with the Ethics Committee, competent authorities, sponsor, and other relevant documents must be kept for at least 10 years (or longer, if required by law). The investigator must take precautions to prevent the accidental or premature destruction of these documents.

During the clinical trial, it is necessary to collect and process medical data from individual patients. Data collection will take place in the involved trial centers. All collected medical data will be entered in the trial centers with the aid of a computer-aided online data collection system and transmitted directly to the Data Management. Name-related identification of individual patients by the Data Management is not required at any time during the clinical trial, as the transfer of patient-related medical data will be carried out using a pseudonym. No features will be transferred that enable immediate identification of specific patients by the Data Management. However, to conduct queries within the framework of the ongoing monitoring of the quality of documentation, it is necessary for the documentation center to assign pseudonyms to specific trial centers.

The data entry, processing and evaluation comply with the provisions of the Data Protection Act. The data managers of the ZKS Jena will have access to all clinical trial data. These persons are sworn to secrecy. The data will be protected against unauthorized access. The monitor, safety-manager and trial statistician will also have access to several clinical trial data.

Privacy statement:

The concerned persons, in whom transmission of their pseudonymized data is necessary, should be informed about the nature of the transmitted data. Persons who disagree with the disclosure of their pseudonymized data will not be included in the clinical trial.

The relevant data protection provisions are complied with.

11 Quality Assurance

The study will be managed by the Sponsor and monitored by Sponsor and its designee in compliance with the Declaration of Helsinki, ICH-GCP, the protocol and all applying local regulations.

11.1 Standardization and Validation

The responsible local laboratories of the trial sites must have a QM system and appropriate internal and external quality assurance measures. Successful participation in external quality assurance measures must be demonstrated by the submission of appropriate proficiency test / accreditation certificates or similar documents. The laboratory tests required for the clinical trial must be GCLP-compliant and follow procedures established in the study manual.

11.2 Monitoring

The monitoring will be done in cooperation with the KKS Halle according to ICH-GCP E6 and standard operating procedures (SOP). Patient recruitment will begin after the initiation visit and all essential documents are available. The monitoring will be done centrally (check of the data entered into the eCRFs by KKS Halle and by means of on-site visits at the respective study center. The frequency of on-site visits depends on the patient recruitment. The monitor's access to the study documents and medical records is ensured by the investigator's agreement and the cooperation agreement between the sponsor and KKS Halle. The KKS Halle guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification (refer also to section 8.2). Initially a formal check of captured information for completeness and plausibility will be done. Thereafter, a check of the correct transfer of data from the source data will be done. The informed consent forms, the inclusion and exclusion criteria and the data related to the primary target variables should be checked completely (100% source data verification). The specific extent of the monitoring and the source data verification will be specified in the monitoring manual.

11.3 Data and Safety Monitoring Board (DSMB)

The data and safety monitoring board (DSMB) is an independent committee composed of a group of individuals (independent physicians/scientists, statistician) with relevant experience in the field of the study. A DSMB will be established to monitor safety data during the course of the clinical study. The composition and responsibilities of the DSMB, and the structure and procedures of its meetings will be laid down in a DSMB manual before inclusion of the first patient. The DSMB will give recommendations to the coordinating investigator for continuation, discontinuation, modification or termination of the study.

11.4 Protocol Deviations

Investigators are not allowed to deviate from the study protocol except under emergency situations when necessary to preserve the rights, safety and well-being of human subjects. Deviations (failures to follow requirements of the study protocol) will be recorded together with an explanation within the eCRF. Investigators should additionally inform the sponsor by mail as in case of serious protocol deviations regarding the safety of the participant. Deviations that impact the rights, welfare, or safety of patients shall be reported to the reviewing Ethics Committees (ECs) as required by local regulations.

11.5 Audits and Inspections

The investigator will permit study-related monitoring and audits, Ethics Committee review and regulatory inspections, providing direct access to source data/documents as ensured by the investigator's agreement and the cooperation agreement between the sponsor and ZKS Jena.

To ensure quality of data and study performance the sponsor may conduct site visits by an independent auditor. An audit will only be performed after notification and arrangement with the investigator. An audit certificate will be issued as quality proof and has to be filed in the study master file and as a copy in the investigator site file. There is a possibility of inspections by the responsible supervisory authority for the purpose of supervision of the ongoing or the

completed clinical study. If an inspection of the study site is announced by the authority, the investigator must inform the sponsor immediately. The investigator ensures immediate access to any study related documents including the original data if requested by a representative of the sponsor (monitor and auditor), the ethics committee or the responsible authorities (regional authority, BfArM).

12 Statistical methods

12.1 Sample Size Estimation

The sample size estimation is based on the primary outcome transplant-free survival (LTX-OS) and two-sided log-rank test. Previous data suggest that type 1 HRS who received TIPS had a 64 % survival at 3 months, with a 20 % one-year survival (Angeli and Gines 2012). In the treatment arms of the RCT in HRS evaluating the combination of terlipressin and albumin, the 3-month transplant free survival rate was 26 % (Martin-Llahi et al. 2008; Sanyal et al. 2008; Boyer et al. 2016; Wong et al. 2021).
Because of the change in the definition of HRS the patients in the present study will be in a slightly better shape, so that an estimated 3-month survival rate of 50 % (exponential parameter 0.231) in the control and 70 % (exponential parameter 0.1189) in the experimental group (resulting in a hazard ratio HR=0.51) are expected. With significance level of 5 %, power of 90 %, recruitment period of 24 months, individual follow-up of 12 months and dropout rate of 10 % (exponential parameter 0.0088) 56 patients are needed in each group. Because of expected additional T-to-C-switcher (patients, randomized in the TIPS-group, but who develop contraindications and therefore are not in constitution for this procedure) between randomization and TIPS procedure 62 patients will be randomized to each group. Although there are no data regarding this, from clinical experience we believe that this will happen in approximately 10 % of patients. As the adjusted Cox regression analysis is more powerful than the log-rank test, this sample size calculation is considered to be conservative. Furthermore, patients who are initially assigned to the C group, may develop during follow-up complications of cirrhosis in which TIPS placement is indicated. There is no clear-cut data about the number of patients in whom this will occur and hence drop in TIPS treatment (C-to-T-switcher). Assuming, that this number will be low, a relatively high power of 90 % was chosen to account for possible switchers, the sample size is calculated without this information.

12.2 Statistical Analysis

12.2.1 Populations for Analysis

The primary analysis data set is the intention-to-treat population. This data set contains all the patients who have been enrolled in the clinical trial and randomized.
The secondary analysis data set is derived from the per-protocol population. This data set includes all patients who have been treated according to the protocol during the whole duration of the study and reached a defined endpoint.
The tertiary analysis data set (safety-population) contains all the patients who have received the trial procedure.

12.2.2 Methods of Analysis

All compiled data will be analyzed at least in a descriptive manner. Including count of compiled data and missings, mean, standard deviation, minimum, quartiles, maximum for metric and frequency analysis for ordinal and categorical data.

Demography: age, sex, size, weight, racial background.

We hypothesize that the 12-month liver transplant free survival is higher in patients in the interventional group. We will test the hypothesis

H0: HR = 1.0 vs. HA: HR ≠ 1.0.

The primary endpoint will be analyzed based on the intention to treat principle using a Cox regression adjusted for AKI stage. Drop-outs will be dealt with as independent right censored in the primary analysis. All patients will be analyzed in their randomization-group. Because both switcher groups are not random inside their groups a per protocol analysis will be performed as sensitivity analysis of the primary outcome. Drop-outs and C-to-T-switcher will be dealt with as independent right censored in this analysis without T-to-C-switchers.
Additional both analyses will be performed with requirement of TIPS implantation/revision in the Follow-Up as third endpoint.

We will perform a competing-risk-analysis in addition to the primary endpoint with the competing events death and Liver-transplantation. As secondary outcomes reversal of HRS-AKI (vs baseline), partial response to treatment (vs baseline), need of renal replacement therapy and recurrence of HRS-AKI at 3 and 12 months will be assessed by logistic regression adjusted for AKI stage. In-hospital, 28-day and 90-day survival will be assessed by logistic regression adjusted for AKI stage. Changes in HrQoL at 3 and 12 months with respect to study baseline will be compared between groups by linear regression adjusted for AKI stage. 3-month liver transplant free survival will be analyzed using a Cox regression adjusted for AKI stage. Development of further decompensations and length of in-hospital-stay will be analyzed descriptively. Results will be interpreted in an exploratory manner.

The Number of AEs and SAEs in each group with special attention on the development of ischemic hepatitis, acute on chronic liver failure, hepatic encephalopathy and signs of heart failure will be analyzed. Laboratory assessments include sodium, potassium, ALAT, ASAT, GGT, AP, Bilirubin, Albumin, INR will be analyzed descriptively as safety parameters.

12.2.3 Subgroup Analysis

The primary endpoint will be analyzed in a secondary analysis based on the intention to treat principle using a Cox regression (with centers, presence/absence of intrinsic renal damage as determined by plasma and urine biomarkers, etiology of the underlying liver disease (alcoholic versus non-alcoholic) and impact of the presence of intrinsic nephropathy as assessed by cystatin C and UnGAL as fixed effects) adjusted for AKI stage. These effects will be checked with BIC (Bayesian information criterion). In case of significance, results will be interpreted in an exploratory manner.

12.3 Definition of Screening Failures, Drop-outs and switchers

Patients who do not meet all inclusion criteria or meet any exclusion criterion are not eligible for randomization and will be considered as screening failures. Patients who for any reason fail to continue in the trial until the last visit are considered as dropouts.

C-to-T-switcher: patients, who are initially assigned to standard of care (Control, C) but develop complications of cirrhosis in which TIPS placement is indicated during follow-up and hence drop in TIPS treatment (T).

T-to-C-switcher: patients, randomized in the TIPS group (T), but who are not in constitution for this procedure or develop contraindications for TIPS procedure between randomization and day of planned TIPS placement, respectively and drop into standard of care treatment.

12.4 Missed visits

It is possible that patients miss to attend one or more visits but can be followed up until the regular end of the study at the 12-months FU. The number of missed visits at the respective time points will be given in the CONSORT 2010 flow diagram.

13 Regulatory and Administrative Issues

13.1 General remarks

This clinical study was designed, will be conducted and reported in compliance with Good Clinical Practice (GCP), and the applicable national laws and regulations and with the ethical principles laid down in the Declaration of Helsinki to assure that the rights, safety, and well-being of the participating subjects are protected.

The Liver-HERO trial is a clinical trial of a medical device that serves to answer scientific questions. Therefore, this study is conducted as a “sonstige klinische Prüfung“ according to § 3 Abs. 4 MPDG in accordance with Article 82 of the European Medical Device Regulation (MDR) and § 47 of the German Medical Device Implementation Act (MPDG) and requires a sponsor (§ 25 MPDG).

13.2 Ethic committees

The study protocol and other associated documents will be submitted to the responsible ethics committee before initiation of the study. In each study site, the clinical study must not be started until the competent local ethics committee has approved the suitability of the study site and the qualifications of the investigators. Additional requirements issued by the EC must be met. Recommendations should be considered and implemented if necessary.

13.3 Regulatory Authority

Before study start the sponsor has to submit a notification (“Anzeige”) to the German Competent Authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) via DMIDS and the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, BfS) by electronic/paper mail.

13.4 Insurance

All patients participating in the trial will have insurance coverage by the sponsor which is in line with the applicable law and regulations, covering in its terms and provisions, its legal liability for injuries caused to participating persons arising out of this research performed strictly in accordance with scientific protocol as well as applicable law and professional standards.

The insurance was taken out at

Newline Europe Versicherung AG, Schanzenstraße 28a, D-51063 Köln Germany (Insurance policy number: NEV050158A

Each patient will get a copy of the conditions of insurance (including coverage of accidents on the way from the patient’s home to the study site and back). Investigators will find the respective conditions and confirmation of insurance in the ISF.

Any impairment of the health which might occur as a consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree with the appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage. During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any AE and additionally drugs taken. The terms and conditions of the insurance will be delivered to the patient. The insurance company has to be informed about all amendments that could affect patient’s safety.

13.5 Amendments

After the commencement of the clinical study, the sponsor may make amendments to the protocol. All changes in documentation will be advertised to the respective competent authorities according the current valid legislation at the respective time point. All planned substantial changes have to be approved by the ethic committee (EC) and the regulatory authority. The implementation of a substantial amendment can only occur after formal approval of EC and the regulatory authority and must be signed by the investigators

Study conduction has to be done according to the study protocol unless it is necessary to take immediate action required for the safety of any patient included in this study. In such cases, the sponsor has to be notified as soon as possible of this action. Protocol violations have to be documented and if applicable explained (see Ch. 11.4). Study conduction has to be done according to the study protocol. In exceptional cases, however, modifications of the study protocol may be necessary. Such changes can only be made if agreed by the sponsor, coordinating investigator, study coordinator and biometrician. Any changes to the study procedures have to be done in writing and must be documented with reasons signed by all authors of the original study protocol. Amendments that require approval have to be submitted to the ethics committee and the competent federal authority and will not be implemented until approval. Not included are protocol deviations to avoid immediate dangers. Any changes of examination and treatment procedures or points of time which are justifiable according to the investigator have to be documented (e.g. as emergency measure on the Case Report Form) giving the reasons and reported to the sponsor immediately.

13.6 Study Reports

The Coordinating Investigator supported by ZKS Jena is responsible for the preparation of the report and submission to the EC and CA.

13.7 Registration

Prior to the beginning of the study, the Coordinating Investigator has registered the trial in a public register which is a prerequisite for publication in a peer-review journal. The study is registered at clinicaltrials.gov (NCT identifier: NCT05346393).

13.8 Funding

The study is entirely funded by the Deutsche Forschungsgemeinschaft (DFG project number 431667134). There is no direct or indirect funding by the manufacturer / distributor of the medicinal product.

13.9 Contracts with sites

Agreements between sponsor and sites cover description of the contractual object, legal frameworks, required approvals & unfeasibility, responsibilities and obligations of both partners regarding all parts of the clinical trial, intellectual property rights, publications, confidentiality statement, warranty coverage and remuneration. Remuneration include a set-up fee independently from patient inclusion and a case-by-case fee, depending on the occurred FU visits. The agreement has to be signed prior to site initiation.

13.10 Study report

The sponsor is responsible for preparation and submission of the final study report which is due within 12 months of study completion (LPLV). No interim analyses and reports are planned. The study report is to be written in compliance with the relevant regulations and guidelines.

13.11 Publication Policy

Publication policy, rights and obligations for this study have been negotiated, detailed and defined in the Investigation Contractual Documents and Agreements with the Investigation Site and Investigators. All publications will ensure privacy rules are met for all patients.

14 Definitions

14.1 Baseline Creatinine

In order to evaluate the presence of AKI, one needs to evaluate the difference with the baseline creatinine. Baseline creatinine is a value of serum creatinine obtained in the previous 3 months, in a stable situation. In patients in whom more than one value in the last 3 months is available, the value closest to the admission time to the hospital should be used. In patients without a previous serum creatinine value, the serum creatinine on admission should be used as baseline (Angeli, Rodriguez, et al. 2015).

14.2 Ascites

Grading of ascites should be done as follows:

- no ascites (in the physical examination)
- ascites
- tense ascites

14.3 AKI

AKI is an increase in serum creatinine from at least 0.3 mg/dL (26.5 µmol/L) or greater within 48 hours or a 50 % increase of serum creatinine from its baseline value which is known, or presumed to have occurred in the prior 7 days (Angeli, Gines, et al. 2015).

AKI Stage	Definition
AKI Stage 1	increase in sCr ≥ 0.3 mg/dL (26.5 µmol/L) within 48h or an increase in sCr ≥ 1.5-fold to 2-fold from baseline[9]
AKI Stage 2	increase in sCr > 2-fold to 3-fold from baseline
AKI Stage 3	increase of sCr > 3-fold from baseline or sCr ≥ 4.0 mg/dL (353.6 µmol/L) with an increase ≥ 0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy

14.4 Refractory ascites

Refractory ascites is defined according to the International Ascites Club criteria, when there is less than 800 gr weight loss over 4 days in patients on low salt diet and high dose diuretics (spironolactone 400 mg/day and furosemide* 160 mg/day), or lower dose of diuretics with complications secondary to the use of diuretics such as hyponatremia, renal failure, hepatic encephalopathy. *equivalent dose of torasemide 40 mg/day. This diagnosis can only be ascertained in a stable patient without complications such as infection or bleeding (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018; Gerbes et al. 2019).

14.5 Recurrent ascites

Patients with recurrent ascites despite low salt diet and adequate dose of diuretics defined by the need of more than 3 paracenteses in three months. This diagnosis can only be ascertained

[9] Baseline means here the time before development of AKI

in a stable patient without complications such as infection or bleeding at the time of paracentesis (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018; Gerbes et al. 2019).

14.6 Diuretic sensitive ascites

Patients with ascites with a high SAAG in whom administration of loop diuretics and mineralocorticoid receptor antagonist (with or without low salt diet) leads to a reduction in body weight have a diuretic sensitive ascites. In these patients less than 3 large volume paracentesis per year are required (European Association for the Study of the Liver. Electronic address and European Association for the Study of the 2018).

14.7 Variceal bleeding

Suspicion of variceal bleeding is defined by the occurrence of acute upper gastrointestinal bleeding with hematemesis or melena or gastric aspirate with blood in patients with cirrhosis. The diagnosis of variceal bleeding is if bleeding signs are seen on a varix (jet, oozing, white nipple) or if blood is seen in the stomach in the first 24 hours after time zero (time of admission) and no other source of upper gastrointestinal bleeding is identified. Clinically significant variceal bleeding is defined by variceal bleeding with at least transfusion requirement of 2 units of blood or more within 24 hour of time zero (time of admission) together with a systolic blood pressure < 100 mmHg and/or a pulse rate > 100 bpm (de Franchis et al. 1992; de Franchis 2005).

14.8 Hepatic encephalopathy

Overt hepatic encephalopathy is defined by the presence of clinically evident altered mental status with disorientation and with or without asterixis. This applies to patients with hepatic encephalopathy grad II-IV in the West Haven Classification. Covert hepatic encephalopathy refers to patients with neuropsychometric and/or neurophysiological disorders without disorientation or asterixis (Bajaj et al. 2011).

West Haven Criteria for grading mental state in patients with cirrhosis

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired addition or subtraction
II	Lethargy or apathy Disorientation for time Obvious personality changes Inappropriate behavior Asterixis
III	Somnolence to semi-stupor Responsive to stimuli Confused Bizarre behavior
IV	Coma, unable to test mental state

14.9 ACLF

Acute on chronic liver failure is a distinct entity with acute decompensation and organ failure (Arroyo, Moreau, and Jalan 2020). Its evaluation is done by means of the EASL-CLIF Consortium organ failure score (European Foundation for the study of chronic liver failure;

https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf). Each organ system function receives a score ranging from 1 point (close to normal) to 3 points (abnormal). The presence of organ failure (in grey on the table) is defined by a score of 3 points and in the case of kidney by the presence of a creatinine greater than 2 mg/dL.

Organ system	1 point	2 points	3 points
Liver	Bilirubin < 6 mg/dL	Bilirubin 6-11.9 mg/dL	Bilirubin ≥ 12 mg/dL
Kidney	Creatinine < 1.9 mg/dL	Creatinine 2-3.4 mg/dL	Creatinine ≥ 3.5 mg/dL
Brain (West Haven Criteria)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR < 2.0	INR 2.0-2.4	INR ≥ 2.5
Circulation	MAP ≥ 70 mmHg	MAP < 70 mmHg	Vasopressor requirement
Respiration	PaO_2/FiO_2 > 300 SpO_2/FiO_2 > 357	PaO_2/FiO_2 201-300 SpO_2/FiO_2 215-357	PaO_2/FiO_2 ≤ 200 SpO_2/FiO_2 ≤ 214

PaO2 = oxygen partial pressure; SpO2 = peripheral capillary oxygen saturation; FiO2 = fraction of inspired oxygen

14.10 AKI-HRS reversal

A full response or HRS-AKI reversal is a return of serum creatinine to a value within 0.3 mg/dL (26.5 µmol/L) of the baseline value (Angeli, Gines, et al. 2015; Sola et al. 2021).

14.11 AKI- HRS partial reversal

A partial response or partial reversal is the regression of the AKI to a serum creatinine ≥ 0.3 mg/dL (26.5 µmol/L) above the baseline value (Angeli, Gines, et al. 2015; Sola et al. 2021).

14.12 HRS recurrence

An AKI-HRS recurrence is defined by a new episode of HRS-AKI in a patient in whom a reversal or partial reversal took place and in whom treatment for HRS was successfully discontinued (at least 48 hours).

14.13 Diastolic dysfunction

Diastolic dysfunction is defined by the presence of at least three abnormal values from the following four parameters (Nagueh et al. 2016):

- annular e' velocity: septal e' < 7 cm/ sec or lateral e' < 10 cm/sec
- average E/e' ratio > 14
- LA volume index > 34 mL/m^2 and
- peak TR velocity > 2.8 m/sec

Patients who have abnormal diastolic function can be further graded according to the E/A Ratio: Grade I diastolic dysfunction is defined by a mitral E/A ratio ≤ 0.8, Grade II > 0.8 to < 2 and grade III by a mitral E/A ratio > 2 (Nagueh et al. 2016).

14.14 Post contrast medium AKI

Development of PC (post contrast)-AKI as defined by an increase of serum creatinine PC-AKI and of ≥ 0.3mg/dl, or of ≥ 1.5–1.9 times baseline (KDIGO definition of AKI) in the 48–72 h following CM administration (van der Molen et al. 2018).

14.15 NYHA Classification

Class	New York Heart Association functional classification

I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

14.16 Milan criteria

The threshold Milan criteria (“Milan in”) are as follows:

- one lesion smaller than 5 cm; alternatively, up to three lesions, each smaller than 3 cm
- no extrahepatic manifestations
- no evidence of gross vascular invasion

If at least one of the criteria is not fulfilled, it is considered as “Milan out”.

14.17 ECOG

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

15 Literature

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