Statistical Analysis Plan[1]

Section 1: Administrative Information

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Revision Control

Protocol version	Updated SAP version number	Section number changed	Description of change	Date changed
V3.1	V1.0			

SAP Signatures

I approve the attached SAP.

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[1] Based on Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017; 318(23):2337–2343. doi:10.1001/jama.2017.18556

Roles and responsibilities

Name	Role	Institution
Grégory Tio	Trial Statistician	CHU Besançon
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Contributions

Maxime Desmarets developed the statistical analysis plan (SAP) based on the analyses set out in the trial protocol. Grégory Tio is the trial statistician and helped answer questions related to trial data and management relevant to the development of the SAP. Maxime Desmarets, Grégory Tio, and Dr Jean-Paul Cervoni reviewed, and approved the SAP.

Abbreviations and Definitions

TIPS	Transjugular intrahepatic portosystemic shunt
GO	Glue Obliteration
GOV	gastro-esophageal varices
MELD	Model of End stage Liver Disease
GV	Gastric Varices
eCRF	electronic Case Report Form

Section 2: Introduction

Background and Rationale

TIPS could have a place to prevent rebleeding after gastric variceal bleeding. It effectively prevents a rebleeding related to portal hypertension as well as numerous complications of cirrhosis. In the single randomized trial comparing glue obliteration to TIPS, TIPS better prevented rebleeding but was associated with a high risk of hepatic encephalopathy and showed no benefit in survival (50). However, survival and post TIPS encephalopathy improved in recent studies using early PFTE-covered TIPS placement. We therefore
assume that early TIPS is the strategy of choice in the management of gastric variceal bleeding. The objective of this study will be to compare demonstrate the superiority of TIPS placement within 72 hours to versus iterative glue obliteration in preventing rebleeding or death after a non-type 1 gastroesophageal gastric variceal bleeding in cirrhotic patients initially treated by glue obliteration.

Our study will be the first large randomized multicenter study to evaluate the 12-month benefit of early TIPS (survival free of rebleeding) in cirrhotics with GV bleeding. In the study by Lo et al., conducted between 1999 and 2004, the TIPS procedure was different from that currently recommended (notably uncovered TIPS) and patients were randomized 3 days after bleeding

control. Thus, rate of early death or rebleeding could not be evaluated and rebleeding within 12 months in the TIPS group was high compared with recent publications. Moreover, in recent studies with early covered TIPS placement, the occurrence of encephalopathy was not different between TIPS group and control group (31, 32, 49). By analogy with early TIPS for the management of esophageal varices, we hypothesize that patients with GV bleeding will benefit from early TIPS. Our trial will evaluate the rate of 12-month survival free of rebleeding and should permit to define the best strategy for the management of GV bleeding.

Objectives

Primary objective:

To demonstrate the efficacy of an "early tips" strategy over glue obliteration (standard treatment) in preventing bleeding recurrence or death at one year after a non type 1 gastroesophageal gastric variceal bleeding in cirrhotic patients initially treated by glue obliteration.

Secondary objectives:

Demonstrate the efficacy of an "early-TIPS" strategy to reduce:
1/ All-cause mortality rate at Days 42 and 365.
2/ Liver related mortality rate at Days 42, 90, 180 and 365.
3/ Rebleeding rate at Days 42, 90, 180 and 365.
4/ Cumulative incidence of complications of cirrhosis at Day 365.
5/ Transfusion requirements at Days 42 and 365.

Describe:
6/ TIPS and glue obliteration complications.
7/ Compliance in each group.
8/ The evolution of liver function at 6 months in each group.
9/ The need for hospitalization in each group during follow-up.
10/ Describe the number of infections and their localizations.

Section 3: Study Methods

3.1 Trial Design

This is an open label, multicenter, randomized, 2-arm parallel-group in a 1:1 ratio, trial to investigate the superiority of an "early tips" over glue obliteration in cirrhotic patients bleeding from gastric varices (non GOV1). The main end-point is death or clinically significant rebleeding during the 12-month follow-up, and randomized patients are followed until the end of the 12-month study period.

Early TIPS procedure in experimental arm (Group A):

- TIPS using covered stent will be placed under general anesthesia and with radioscopic guidance by experts.
- The procedure should be performed as soon as possible after randomization and before Day 4.
- Portal pressure should be taken at the time of TIPS insertion, with a goal of hepatic venous pressure gradient of less than 12 mmHg at the end of the procedure.
- Embolization of collaterals will not be authorized in the present study.

Glue obliteration procedure in control arm (Group B):
- Filling of varice(s) with tissue adhesive under endoscopic guidance will be initially performed in all patients under general anesthesia. The use of a Doppler EUS will be at the discretion of the practitioner.
- Endoscopic control (and further glue obliteration session if necessary) will be performed in the group B between day-5 and day-8 after the initial bleeding. A new session will then be proposed at days 42+/-7, 90+/-14, 180+/-14 and 365+/-14.
- Endoscopic reports will be systematically collected. The report should specify the topography and size of varices (if possible, a picture will be collected), the type of glue, the volume injected as well as the proportion of Lipiodol.
- In the case of coexistence of esophageal varices, the latter will be systematically treated during the same endoscopic session by band ligation.
- In patients randomized to group B the decision of "salvage TIPS" will be left to the discretion of the investigator and will be then considered as a failure of the endoscopic procedure.
- When placing TIPS for another indication during follow-up in the group B, the patient will be censured at the date of installation of the device.
- In the absence of contraindication, a non-selective beta-blocker treatment will be proposed in the group B according to the recommendations of the Baveno VI Consensus Workshop 2015 (14).

3.2 Randomization

The trial used a centralized interactive web response system (IWRS) to perform patient allocation (CleanWeb software, Telemedecine Technologies, Boulogne-Billancourt, France). The data manager for the study prepared the randomization schedule for each clinical site participating in the trial. The randomization schedule has the following characteristics: 1. Stratified by center; 2. blocks of size four with equal numbers of patients assigned to the early-TIPS or glue obliteration within each block. The block size was only known by the senior statistician and the data manager of the study.
Only study-certified clinic staff with individually assigned userid/password can access the randomization application. Only participants meeting the inclusion/exclusion criteria according to data entered in the eCRF
system, are listed among the participant IDs eligible for randomization. The date and time of the completion
of the randomization treatment assignment is the time of study entry for each patient.

3.3 Sample size

The sample size is calculated with a projected rate of composite event of failure at 12 months of 15% in the group “TIPS” [estimated from Garcia Pagan, New Engl J Med 2010] versus 40% in the group « glue» [estimated from Hou, Gastrointest Endosc 2009].
A number of 52 patients in each group will achieve 80% power to detect TIPS superiority using a one-sided logrank test at a 0,050 significance level, with a proportion dropping out of both groups of 10%.
Total number of scheduled patients recruited or observations collected: 104.

3.4 Timing of final analysis

The trial is scheduled to end with the final 12-month follow-up appointment. The data will be cleaned, verified and locked. Final analysis will begin once the principal investigator has confirmed the final database.

Section 4: Statistical Principles

4.1 Confidence Intervals and P-values

All tests will be two-sided, with p values of less than 0.05 denoting statistical significance. 95% confidence interval will be used to report effect estimates of secondary endpoints.

4.2 Adherence and protocol deviations

The list of protocol deviations will be established and the reasons for non-evaluable cases will be indicated as following:

• Inclusion criteria not satisfied.
• Deviations related to the procedure administration

4.3 Analysis populations

The primary analysis will be performed according to the intention-to-treat (ITT) principle.

Modified intention to treat population (mITT)
The mITT population will consist of all eligible randomized patients in the treatment group assigned by the randomization, irrespective of whether the patient underwent the procedure allocated by randomization or if crossovers occurred. Randomized patients who were later found to not meet inclusion criteria will not be included in the mITT population.

Per protocol population
This population will include all randomized patients with the exception of patients who could not undergo the procedure the patients were assigned to including TIPS failure. Randomized patients who were later found to not meet inclusion criteria will not be included in the per protocole population.

Safety population
By default, patients who underwent the procedure after randomization will be included in the safety population and assigned to the glue obliteration arm. Patients who underwent the early-TIPS procedure without regard for its successful completion will be included in the safety population and assigned to the early-TIPS arm. Patients who, for any reason, could not undergo either procedure will be excluded from the safety population.

Section 5: Trial Population

5.1 Eligibility

Inclusion criteria:

- Age ≥ 18 and ≤ 75 years.
- Cirrhotic patients with variceal bleeding from gastroesophageal gastric varices type 2 or isolated gastric varices type 1 or 2 (Sarin classification) according to the following criteria: endoscopic signs of an active spurting or oozing from gastric varices (GV); adherent blood clots, white nipple signs, or erosions on the GV and absence of other bleeding sources. Cirrhosis: The diagnosis of liver cirrhosis is based on previous liver biopsy or on the combination of clinical, biochemical, and radiological findings. If biopsy findings are unavailable and in case of non-complicated cirrhosis, non-invasive markers will be used.
- Hemodynamically stable patient without clinically significant rebleeding (Baveno criteria) within 12 hours after the initial endoscopy with glue obliteration.
- Written informed consent obtained.
- Patient affiliated to a social security system.

Exclusion criteria:

- Pregnant woman or breastfeeding.
- Minor and patients older than 75 years.
- Hepatocellular carcinoma outside the Milan criteria or other cancer at a palliative stage.
- Non cirrhotic portal hypertension.
- Child Pugh score > 13.
- History of severe or refractory hepatic encephalopathy unrelated to gastrointestinal bleeding.
- Congestive heart failure.
- History or presence of pulmonary hypertension.
- Patient with other indication for TIPS.
- Uncontrolled gastric variceal bleeding.
- Portal vein cavernoma.
- Patient who have previously received a TIPS procedure.
- Failure to receive clear information in patients without an identified trusted person.
- Refusal of the participation agreement by signing the information form and consent as defined.
- Exclusion period from another biomedical study

A list of ineligible cirrhotic patients and the reasons for their ineligibility was created in each participating center. This list will allow us to document the representativeness of the study sample.

5.2 Withdrawal/Follow-up

Criteria for stopping the study are:

- withdrawal of consent,
- liver transplantation,
- loss to follow up,
- enrollment of ineligible subjects.

Patients withdrawn from the study for withdrawal of consent, liver transplantation or loss to follow up will be censored at the date of withdrawal. Ineligible subjects will be excluded from the mITT analyses. Unless consent to analyze data is also withdrawn, all the data collected prior to withdrawal from the study will be considered for analysis.

5.3 Baseline Patient Characteristics

The description and initial comparison of randomized groups will focus on:
- Patient information: demographic characteristics, clinical exams, place of support, medical history, radiological exams, diagnosis of cirrhosis, cause and complications of cirrhosis, hepatocellular carcinoma, and concomitant treatments
- Endoscopic characteristics of initial bleeding: endoscopic condition, lesion responsible for bleeding, pre-existing treatment
- Biological results at admission: virology, hematology, blood biochemistry, arterial blood gas, bacteriology, ascites puncture, plasma
- Scores: Child-Pugh, MELD, MADDREY

Quantitative variables will be in the form of a table showing the number of values and the number of missing data, the mean and median, standard deviation, coefficient of variation, the minimum and maximum for each group and for the overall population.
Categorical variables will be in the form of a table revealing the number of values and the number of missing data, the percentage of each category and the confidence intervals for each group and for the overall population.
Continuous variables will be compared using Student's t-test or the Mann-Whitney test, as appropriate. Categorical variables will be compared using the Chi-squared test or Fisher's exact test, as appropriate.

Section 6: Analysis

6.1 Outcome Definition

Primary endpoint
Death (all cause) or clinically significant rebleeding (upper gastrointestinal bleeding whatever its origin, with event date) during the one-year follow-up.

Secondary endpoints
1- Survival at Days 42, 90, 180 and 365.
2- Incidence of liver related death at Days 42, 90, 180 and 365.
3- Incidence of significant rebleeding at Days 42, 90, 180 and 365.
4- Cumulative number of packed red blood cells required by each treatment arms.
5- Incidence of complications of cirrhosis during the 12-month follow-up.
- any of the complication below
- bacterial infections,
- jaundice,
- ascites,
- spontaneous bacterial peritonitis,
- hepatic encephalopathy,
- hepatorenal syndrome,
- further decompensation.
6- Frequency of:
- TIPS technical failure and TIPS complications: thrombosis, heart failure, infection and encephalopathy.

- Technical failure of GO and complications of GO: migration of glue, infection of the site of injection, significant bleeding during the procedure (hospital stay, blood transfusion, 3 g drop in hemoglobin).
7- Number of patients lost to follow up at Day 365 in each group
8- Change of MELD score between inclusion and Day 180 in each group.
9- Number of days spent in hospital in each group during the 12-months follow-up.
10- Number of bacterial infections and localizations.

Definitions

Liver-related death as defined in Asrani et al. (Gastroenterology. 2013 ;145 :375–82.e1–2) **:** death with any of the following causes identified.

Disease category	**ICD-10 codes**
Hepatitis C virus	B171, B182
Other hepatitis	B15, B16, B170, B172, B178, B179, B180, B181, B188, B189, B19, K73
Primary liver cancer	C22
Secondary liver cancer	C787
Esophageal varices	I85
Alcoholic liver disease	K70
Hepatic failure	K72
Liver cirrhosis	K74
Other diseases of liver (toxic, inflammatory, and others)	K71, K75, K76

Significant rebleeding will be defined by Baveno criteria as a recurrent melena or hematemesis resulting in any of the following:
- Hospital admission
- Blood transfusion
- 3 g/dL drop in hemoglobin.

Bacterial infection: hospitalization for bacterial infection by the specified time point
Jaundice: defined as total bilirubin > 50 µmol/L
Ascites: persistent ascites at the specified timepoint.
Spontaneous bacterial peritonitis: defined by an ascitic fluid polymorphonucleated (PMN) cell count of ≥250/mm.
Hepatic encephalopathy (HE): HE is a brain dysfunction caused by liver insufficiency and portosystemic shunting. HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations. Clinical HE is grading according to the West-Haven criteria.
Hepatorenal syndrome (HRS) is essentially a diagnosis of exclusion (i.e., there is an absence of other identifiable causes of renal failure). The hepatorenal syndrome is characterized by the following features in a patient who has established or clinically evident chronic liver disease:

i. diagnosis of cirrhosis and ascites;

ii. diagnosis of AKI according to ICA-AKI criteria: increase of at least 0.3 mg/dL (26 µmol/L) and/or ≥ 50% from baseline, within 48 h;
iii. no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight);
iv. absence of shock;
v. no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.);
vi. and no macroscopic signs of structural kidney injury, defined as absence of proteinuria (> 500 mg/d), absence of microhematuria (> 50 red blood cells per high power field) and normal findings on renal ultrasound.

Further decompensation as defined in the Baveno VII conference: a second (or recurrent) portal hypertension-driven decompensating event (ascites, variceal hemorrhage, or hepatic encephalopathy) and/or jaundice, or the development of spontaneous bacterial peritonitis (SBP) and/or hepatorenal syndrome (HRS-AKI).

6.2 Analysis Methods

Analyses of all endpoints will be performed on the mITT as well as the per protocol population unless specified.

Primary composite endpoint

The Kaplan Meier method will be used to estimate rate of composite event over the 12-month follow-up. The composite event rates will be compared between study arms using the log-rank test. Hazard ratio for composite event rate (TIPS vs. GO) and its 95% confidence interval will be determined using a Cox proportional hazard model. In this model, a center effect will be tested as well as interaction between treatment and center. The assumption of proportional hazards will be tested using Schoenfeld residuals and if violated, the model will be fitted with a treatment-time interaction or a time-varying covariate, as appropriate.
The composite event rate at 12 months will be described according to a number of covariates including age, gender, and specific liver scores (Child-Pugh and MELD) to examine their potential effects. Each of these factors will be analyzed statistically using a Cox proportional hazard model incorporating terms for treatment strategy, the covariate and the strategy-by covariate interaction.
The number of patients with composite event, estimated hazard ratios, and associated 95% confidence intervals will be calculated within each of the subgroups generated by these analyses.

Covariate	**n**	**No. Events**	**Treatment effect HR - 95%CI**	**P value**
Intervention				p
Glue obliteration			Ref	
Early TIPS			Treatment effect	
Subgroup analyses				
Age				P*
<median			<median effect	—

>median			>median effect	—
Sex				P*
Male			Effect in men	—
Female			Effect in women	—
Child Pugh score				P*
B			Effect in B patients	—
C			Effect in C patients	—
MELD				P*
<median			<median effect	—
>median			>median effect	—
EH upon admission				
No				
Yes				
High risk patients (Child-Pugh C, or Child-Pugh B with active bleeding)				
Not high risk			Effect in not high-risk patients	—
High risk			Effect in high-risk patients	—
Shock				P*
No shock			Effect in patients with shock	—
Shock			Effect in patients without shock	—
ACLF upon admission†				P*
Grade 1				—
Grade 2				—
Grade 3				—
Red blood cell transfusion during initial hospitalization				P*
0			Effect in untransfused patients	—
1-2			Effect in transfused patients 1-2 RBC units	—
>2			Effect in transfused patients with more than RBC units	—

* p value for interaction
† ACLF: Acute on Chronic Liver Failure**; Grade 1:** a) Single kidney failure, b) Single liver, coagulation circulatory or respiratory failure + creatinine 1.5-1.9 mg/dL and/or HE I-II, c) Single cerebral failure (HE III-IV) + creatinine 1.5-1.9 mg/dL; **Grade 2:** 2 organ failures; **Grade 3:** 3 or more organ failure score.

The win ratio method (Pocock et al. Eur Heart J. 2012 Jan;33(2):176-82) will also be applied in order to determine the least effective procedure when giving priority to the more clinically important event (death).

Secondary endpoints

Survival at Days 42, 90, 180 and 365

The survival rates will be compared with the same methods as described above for the analysis of composite event rate.

Incidence of liver related death at Days 42, 90, 180 and 365.

The association of study arms with rebleeding hazard function will be tested using univariate and multivariate Cox models. The cumulative risk of rebleeding during follow-up in each arm will be estimated by calculating the cumulative incidence function (CIF) rebleeding at 12 months. In this approach, death for other causes during follow-up will be considered as a competing event.

Incidence of rebleeding during follow-up
The association of study arms with rebleeding hazard function will be tested using univariate and multivariate Cox models. The cumulative risk of rebleeding during follow-up in each arm will be estimated by calculating the cumulative incidence function (CIF) rebleeding at 12 months. In this approach, death free of rebleeding during follow-up will be considered as a competing event.

Incidence of the other complications of liver cirrhosis during follow-up
The association of treatment group with the hazard function of other complications will be tested using univariate and multivariate Cox models. The cumulative risk of other complications during follow-up in each arm will be estimated by calculating the CIF at 12 months. In this approach, death free of complications during follow-up will be considered as a competing event.

Cumulative number of packed red blood cells required by each treatment arms.
Variation of MELD score between inclusion and 6 months in each arm
Number of days that patients spend in hospital during follow-up
Comparison between strategy groups will be performed with Student's t-test or the Mann-Whitney test, as appropriate.

Frequency of TIPS technical failure and TIPS complications: thrombosis, heart failure, infection and encephalopathy. Frequency of technical failure of GO and complications of GO: migration of glue, infection of the site of injection, significant bleeding during the procedure (hospital stay, blood transfusion, 3 g drop in hemoglobin).
This analysis will be performed on the safety population.

6.3 Missing Data

In general, missing values will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data analyses and presentations.

Survival analysis
All patients not reaching any event at the end of follow-up or before their last assessment (for patients lost to follow-up) will be censored at the date of their last assessment visit. Patients receiving a liver transplant will be censored at the time of liver transplantation.

6.4 Harms

Safety analyses will be conducted in the safety population using the same evaluation period as for efficacy analyses (i.e. from randomization until end of 12-month follow-up).
The number of adverse events and SAE observed in each strategy group will be described and compared by using Chi-squared test or Fisher's exact test, as appropriate. Adverse events will be described in a table in order of decreasing frequency.

6.5 Software

Statistical analyses will be performed by the CIC INSERM 1431 on SAS/STAT 9.4 for windows (SAS Institute, Inc., Cary, NC)