Trial Synopsis

High-dose intravenous silibinin infusions during 10 days as add-on treatment to triple therapy (telaprevir, peginterferon alpha and ribavirin) in cirrhotic GT 1 hepatitis C virus infected patients being null responders to prior dual therapy with peginterferon alpha and ribavirin – a proof-of-concept trial on antiviral efficacy and safety

A phase 2a proof-of concept study, randomized, controlled, open-label, 2-armed

(HISTORY)

Name of Finished Product / Name of Active Substance:
Legalon© SIL / silibinin
Incivo© / telaprevir
Pegasys© / peginterferon alpha 2a
Copegus© / ribavirin

Indication / Diagnosis:
Chronic hepatitis C

Phase of Development:
Phase 2a

EudraCT-Number: 2012-004442-15

Registry-Number: DRKS00005455

Date of version: 03.12.2014
Version of report: final 1.0

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Date of first enrolment: 12.12.2013
Date of last completed: 03.03.2014

Signatures

With their signatures, the signing authors agree with the contents of presented report. The presented clinical trial was performed according to the principles of the Declaration of Helsinki, Good Clinical Practice and according the applicable legal requirements.

Legal representative of the sponsor and principal investigator	Thomas Berg, Prof. Dr.	16/12/2014 Date
Biometry	Annegret Franke, Dr.	03.12.2014 Date
further authors:	Anett Schmiedeknecht, Dr.	03.12.2014 Date

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1 Name of the sponsor

Universität Leipzig
Ritterstr. 26
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Authorised representative of the sponsor:
Prof. Dr. Thomas Berg

2 Name of Finished Product	3 Name of Active Substance
Legalon© SIL	**Silibinin**
Incivo©	telaprevir
Pegasys©	peginterferon alpha 2a
Copegus©	ribavirin

Table 1: information on the trial products

4 Individual trial table

not applicable

5 Title of Study

High-dose intravenous silibinin infusions during 10 days as add-on treatment to triple therapy (telaprevir, peginterferon alpha and ribavirin) in cirrhotic GT 1 hepatitis C virus infected patients being null responders to prior dual therapy with peginterferon alpha and ribavirin – a proof-of-concept trial on antiviral efficacy and safety
Version of trial protocol: final 2.0 from September 30th, 2013.

There has been one major amendment to the clinical trial:

No.	Favourable opinion by ethics committee	Authorisation by competent authority	Contents
01	27.01.2014	18.12.2013	Amendment in the course of the initial trial application: • Change of coordinating investigator • Change in definition of virologic stopping rules • Addition of the medical consultant • Adaptation of laboratory analyses

Table 2: dates of approval and contents of amendment during trial implementation

6 Investigators	7 Study centre(s)

The list of investigators and study centers is found in the appendix (chapter 22.1)

8 Publication (reference)

There have been no publications from the HISTORY trial.

9 Studied period (years)

Date of first enrolment: 12.12.2013
Date of last completed: 03.03.2014

The study was aborted prematurely due to current developments in the field of treatment of chronic hepatitis C patients (i.e. approval of new antiviral agents).

10 Phase of development

The HISTORY trial was a phase 2a trial.

11 Objectives

11.1 Primary Objective

To compare the rates of RVR – rapid virological response, defined as HCV RNA ≦ LOQ (limit of quantification), defined as ≤ 15 IU/mL at week four of an antiviral treatment with telaprevir, peginterferon alpha and ribavirin – between patients who either receive infusions of silibinin during the first ten consecutive working days of antiviral treatment or no infusions.

11.2 Secondary Objectives

To compare the rate of patients with undetectable HCV-RNA (LOQ ≤ 15 IU/mL) at week 12, 24 and 48 (end of treatment - EoT; oTVR-12/24/48) of antiviral treatment
To compare the rate of patients with undetectable HCV-RNA at week 12 and 24 of Follow-Up (SVR-12/24)
To assess intensive viral kinetics during silibinin treatment (either in arm A or B)
- the time needed to achieve negative HCV RNA levels
- the extend of HCV RNA level reduction with every silibinin infusion

To compare the safety profile of both study arms the causally related AE and SAE to study medication, the rate of decompensated liver function as well as biochemical findings will be assessed.
To assess the emergence of viral resistance mutations against telaprevir and / or silibinin in patients with viral break-through or incomplete virological response during antiviral treatment.

12 Methodology

This phase 2a, randomized, controlled, open-lable 2-armed proof-of-concept study was designed to evaluate the therapeutic benefit of a quadruple therapy with silibinin infusions, telaprevir, peginterferon alpha and ribavirin.
Patients were planned to be randomized in a 2:1 ratio in favour of the active arm using stratification according to:

- HCV genotype 1a versus 1b (versus GT 1 but subtype not estimable) and
- Prior treatment with an HCV specific protease inhibitor versus no prior treatment with an HCV specific protease inhibitor

...with potentially different prognosis

13 Number of patients (planned and analysed)

The aim was to include a total number of 30 patients with evaluable data with regard to the primary (and secondary) endpoints. It was assumed that a dropout rate of <5 % during the

first four weeks (before the primary endpoint was reached) will be reached. A total number of about 33 patients should be recruited.

A total of 3 patients were to be included in the screening process of whom only one was eligible for randomisation and was randomised in the control arm. However, he/she terminated the study before the end of regular follow up time. Since only one patient was treated and none observed until the end of the planned observation period neither a detailed description of statistical procedures planned nor data tabulations and comparisons of treatment groups were provided within this report. A short summary of the only patient is be given regarding her socio-demographic characteristics and course of trial (see below). Adverse events are reported in sec. 20.2.

The patient with Pat-ID 002-6 was screened on December, 12th, 2013 and gave her informed consent to participate at the same day. She was randomized on January, 09th, 2014 to the reference arm and terminated the trial prematurely on the decision of the treating investigator without a rescue treatment on March, 03rd, 2014. The following comment was given: "keine Rescue-Therapie möglich lt. Protokoll, bereits Relapse unter derselben Therapie 2012, außerdem Tripletherapie nicht mehr empfohlen". The patient declined to continue with further FU visits.

Her socio-demographic and disease-describing characteristics were:
- Caucasian race, female beyond the age of gravidity, body height/ weight 1.62 m/ 77 kg, systolic/diastolic blood pressure 162/94 mmHg, heart rate 78/s at screening, year of birth 1959;
- Year of hepatitis C diagnosis in 2008 with earlier Peg/Riba treatment 7/2008-7/2009 but no response;
- HCV-RNA at screening 1850 kU/mL; irrelevantly abnormal leukocytes, thrombocytes, alkaline phosphatase, ASAT, ALAT, γ-GT and glucose values but other lab values within normal ranges.
- With regard to the stratification genotype 1b was detected, no previous treatment with DAA was applied. The randomisation resulted in an allocation to Arm B (reference arm with rescue-therapy acc. to study protocol, if applicable).

14 Diagnosis and main criteria for inclusion

Patients should meet all of the following inclusion criteria:

1. Male or female, age from 18 to 70 years (extremes included)
2. Chronic hepatitis C infection of genotype 1, confirmed by genotypic testing at screening
3. Compensated liver cirrhosis (Child Pugh A) assessed by either
   liver histology: Metavir 4 in a liver biopsy (any biopsy result will be accepted regardless of its age)

or

   non-invasive elastography: a Fibroscan© measurement of >14.5 kPa with an interquartile range (IQR) of less than 20% of the value and a success rate of at least 85%. At screening the Fibroscan testing should not be older than 6 months.
4. Null response to a prior treatment regimen with peginterferon alpha and ribavirin defined as one of the following: <1 log10 drop at week 4 and/or <2 log10 decline of HCV RNA at treatment week 12 or an absolute viral count of ≥30.000 IU/ml at treatment week 12.
5. A) Female patients who are
   - infertile with documentation, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy)
   - postmenopausal for longer than 2 years at screening

- completely abstinent from sexual intercourse
- having sexual intercourse with female partners only or with a vasectomized male partner (bilateral vasectomy at least 6 months prior to screening)
- of childbearing potential and must use two highly effective contraceptive methods. Accepted examples are: Condom with spermicide, diaphragm or cervical cap with spermicide, intrauterine device.

Female subjects may continue to use hormonal contraceptives during administration of study drug. Due to potential drug to drug interactions with telaprevir hormonal contraceptives may be less effective and are not an accepted contraceptive method during the study. Female subjects must continue to use effective contraceptive methods until at least 4 months after the end of dosing.

B) Male patients who are sterile (documented bilateral vasectomy at least 6 months prior to screening) or who agree to abstain from sexual intercourse or who are sexually active with male partners only or with female partners who are not of childbearing potential. Male subjects with female partners of child bearing potential must use two accepted contraceptive methods as listed in 5. A). In addition hormonal contraception in female partners of male study subjects is accepted. Male subjects must continue to use effective contraceptive methods until at least 7 months after the end of dosing.

6. Willing and able to give written informed consent prior to any study related procedure.

No inclusion was allowed, if any of the following exclusion criteria was fulfilled:

1. Chronic hepatitis C with non-genotype 1 infection or mixed infection containing a genotype 2, 3, 4, 5 or 6
2. Detection of resistance associated viral mutations (RAV) in a population based sequencing analysis of the hepatitis C virus NS3/4A region at screening. RAVs are defined as any detected mutation: V36A/G/M, T54A/S, R155G/K/M/T und A156F/N/S/T/V.
3. Positive testing for HIV-1 or HIV-2 antibodies, positive testing for HBs-Ag at screening
4. Evidence of liver disease due to causes other than hepatitis C infection
5. Decompensated liver disease or history of decompensated liver disease: Ascites, bleeding from esophageal varices, portal vein thrombosis, spontaneous bacterial peritonitis, hepatic encephalopathy.
6. Total bilirubin levels of > 1.8 mg/dL (> 1.5*ULN); INR > 1.26.
7. Combined: albumin levels < 30 g/L **and** thrombocyte count < 100/nL (Fontaine et al. 2013)
8. Hematologic lab values out of acceptable ranges:

- Thrombocyte count <80/nL.
- Hemoglobin <12.0 g/dL for men and <11.0 g/dL for women.
- Absolute neutrophil count (ANC) of <1/nL

9. Active or suspected nonhepatic malignancy or history of malignancy within the last 5 years – patients with hepatocellular carcinoma that is solely localized to the liver can be included at the judgement of the investigator.
10. Impaired renal function defined as creatinine levels - female: > 1.8 mg/dL; male: > 2.0 mg/dL
11. Impaired thyroid gland function – TSH outside 0.2 – 4.5 mU/L
12. Body Mass Index <16 or >35 kg/m^2.
13. Female patients who are pregnant or breast feeding or male patients whose female partner is pregnant.
14. History of alcohol or drug abuse (except cannabis) within the past 12 months.
15. History of severe or uncontrolled psychiatric disease, especially depression, including a prior suicidal attempt.

16. Active autoimmune disease, including autoimmune hepatitis; i.e. ANA-Titers > 1:320 at screening.
17. Organ transplantation (exception: cornea or hair transplant)
18. Poor or restricted access to the venous system – patients will receive an i.v. catheter at all silibinin visits.
19. Usage of any investigational drugs within 30 days prior to enrolment
20. Any condition or comorbidity that is listed as contra-indicative for the use of Peginterferon, Ribavirin or Telaprevir – for a detailed list refer to the current SmPC of the respective medication.
21. Inadmissible concomitant medication that is known to be a strong inducer, inhibitor or substrate of cytochrome p450 subtype 3A4.
22. Known allergies to any of the used study medication or their additives.
23. Persons that are imprisoned due to judicial or administrative order

15 Test product, dose and mode of administration, batch number

Note!
The use of peginterferon alpha 2a and ribavirin is currently equal to guidelines-compliant basic medication in the treatment of chronic hepatitis C.

1. Generic Name:	**silibinin = test product**
Trade Names and manufacturer:	Legalon © SIL; Rottapharm Madaus GmbH, Colonia Allee 15; 51067 Köln
2. Generic Name:	**telaprevir**
Trade Names and manufacturer:	Incivo©; Janssen-Cilag GmbH Johnson & Johnson Platz 1 41470 Neuss
3. Generic Name:	**peginterferon alpha 2a**
Trade Names and manufacturer:	Pegasys©; Roche Pharma AG Emil-Barell-Straße 1 79639 Grenzach-Wyhlen
4. Generic Name:	**ribavirin**
Trade Names and manufacturer:	Copegus©; Roche Pharma AG Emil-Barell-Straße 1 79639 Grenzach-Wyhlen

Silibinin - dosing and infusion schedule:
Each patient receives 20 mg silibinin per kg body weight dissolved in 500 ml NaCl 0.9% (usually) on ten consecutive working days at trial site. It is recommended to start silibinin treatment on a Monday according to the predefined treatment regime: two cycles of five days silibinin infusions interrupted by two days non-treatment. Thus silibinin infusions will be administered on days 1, 2, 3, 4, 5, 8, 9, 10, 11 and 12 of antiviral treatment with peginterferon alpha, ribavirin and telaprevir. A dose adjustment of silibinin is not allowed. Criteria for the termination of silibinin infusions are not pre-specified but at the assessment of the investigator. Mild to moderate and isolated elevation of bilirubin levels are not necessarily indicative for treatment termination. If clinical or laboratory findings are suggestive of impaired liver function or decompensation of liver cirrhosis, the investigator at site should discuss the individual case with the coordinating investigator.
The silibinin solution will be administered as scheduled during a period of 2 to 4 hours infusion with a constant flow. Every infusion should include a test phase of 3 to 5 minutes after which the infusion is paused for 5 minutes. Only if the patient feels well it should be continued. It is recommended to start the first infusion in a supine position to avoid hypotensive or orthostatic reactions. The patient should be informed upfront about the expected reaction of skin warming in the beginning of each infusion and about the likely induction of bowel movements during infusion. For this situation the toilet should be easily accessible for the patient and the infusion stand should be on rolls. In case the patient complains about side effects the infusion should be paused and restarted later. Nausea can be treated with oral metoclopramide in accordance with its label.
In general, the following medications will be distributed to the patients at the baseline visit and at further indicated visits; the patient is instructed to take or apply the medication by himself.
Telaprevir:
Telaprevir is dosed as three tablets of 375 mg every 12 hours (1125 mg BID) for oral ingestion after a meal that contains fat. Dose modifications or interruptions are not allowed. Once telaprevir is paused for 24 hours a restart of telaprevir is prohibited. Missed doses can be taken with delay within four hours of the planned intake. After four hours the patient should omit the telaprevir intake and wait for the next scheduled dosing. The planned treatment duration is 12 weeks.

16 Duration of treatment

Arm A: (20 patients) Silibinin infusions (20 mg/kg bw/d) on 10 consecutive working days (ideally Monday to Friday sparing the weekend)
+Telaprevir 1125 mg BID for a period of 12 weeks starting at baseline visit
+ Ribavirin 1000 or 1200 mg (depending on the body weight) divided in two daily doses for a period of 48 weeks starting at baseline visit
+ Peginterferon alpha 2a 180 µg s.c. qweek for a period of 48 weeks starting at baseline visite.
Arm B: (10 patients) Telaprevir 1125 mg BID for a period of 12 weeks starting at baseline visite
+ Ribavirin 1000 or 1200 mg (depending on the body weight) divided in two daily doses for a period of 48 weeks starting at baseline visite
+ Peginterferon alpha 2a 180 µg s.c. qweek for a period of 48 weeks starting at baseline visite.

17 Reference therapy, dose and mode of administration, batch number

See chapter 16 – Arm B

18 Criteria for evaluation

The rapid viologic response (RVR) rate - assessed at week 4 of the combined antiviral treatment – was planned to be used as primary end point (pEP) of the trial.
RVR, defined as HCV RNA ≤ LOQ (limit of quantity, ≤15 IU/mL) should be assessed for every patient in a binary manner (Yes/No). The rate of patients in both treatment arms was planned to be used in confirmatory analysis. For patients without valid HCV RNA values at week 4 conservative missing value imputation was planned be used to get a pEP.

Efficacy endpoints

- rate of patients with undetectable HCV-RNA (defined as ≤15 IU/mL) at week 12, 24 and 48 of antiviral treatment *(→ on-Treatment Virologic Responses – oTVR-12, -24 and -48)*
- rate of patients with undetectable HCV-RNA at week 12 and 24 of follow-up *(Sustained Virologic Response: SVR-12 and -24)*
- rate of patients with normalized ALT (≤ Upper Limit of Normal: ULN; male: ≤50 U/l, female ≤35 U/l) during antiviral treatment to be compared between groups at week 4, and to be reported for the both arms at weeks 12 and 48
- time of treatment needed until normalization of ALT is achieved to be compared between groups at week 4

To describe viral kinetics during the phase of silibinin infusions:

- time until - for the first time - negative HCV RNA (≤ LOQ, i.e. 15 IU/mL) level is detected to be compared between groups at week 4
- number of silibinin infusions needed until – for the first time - negative HCV RNA level is detected to be reported for the arm A
- Area under Curve (AUC) of HCV RNA reduction until week 4 (i.e. completion of silibinin treatment in arm A; the 2 days of weekend were considered via linear interpolation between levels of preceding Friday's and following Monday's measures to be compared between groups

- decline of HCV RNA per single silibinin infusion, calculated via AuC until the respective day divided by number of infusions applied until the preceding day to be reported for the arm A and those patients of arm B who received the rescue treatment

Safety endpoints

- rate of causally related AE, for all 4 IMPs assessed and analyzed separately until visit FU12 (the first visit after EoT with Peg/Riba :end of event reporting period - EoER),
- rate of causally related SAE, for all 4 IMPs assessed and analyzed separately until visit FU12 (EoER),
- rate of decompensated liver function, aggregated until EoS; assessed from following clinical findings
  - development of ascites ***or***
  - development of hepatic encephalopathy ***or***
  - bleeding from esophageal varices

  (Any event of these defines decompensation of liver function.)

  or pathologic values of single biochemical measures
  - reduced albumin level of <25 g/L ***or***
  - elevated INR > 1.63

(Any event of these defines decompensation of liver function)
or combined biochemical measures
- increased bilirubin > 5*ULN (corresponds to >6 mg/dL) ***and***
- increased ALT >5* UNL (corresponds to >250 U/L in males and >175 U/L in females) ***and*** >2*ALT_{BL} (compared to individual initial ALT).

19 Statistical methods

19.1 Primary endpoint analyses

Since only one patient was randomised no confirmatory analysis as described within the study protocol could be performed.

Her HCV-RNA level developed from 1850 kU/mL (V1) over 3080 (V2), 1.74 (V4), 0.3 (V6) to 0.02 kU/mL under the reference treatment.

19.2 Secondary endpoint analyses

The number of patients included was insufficient to compare both treatment arms.

Her lab levels of secondary interest developed from:
- Bilirubin [mg/dL]: 0.47 (V2), 0.7 (V4) to 1.7 (V6) with missing value at V8, but assessd to be normal from V4 to V8;
- ALAT [U/L]: without any measure but assessed as irrelevantly abnormal;
- Albumin [g/L]:_46 (V2), 49 (V4),to 40 (V6) with missing value at V8, but assessd to be normal from V4 to V8;
- INR: stable 1.1 (from V2 to V6) with missing value at V8

20 Summary – Conclusions

20.1 Efficacy Results

None regarding a comparison of arms.

20.2 Safety Results

13 AEs occurred to the only patient included of whom 7 where unrelated to any IMP of the trial. Lists are provided in tables 1 and 2 with regard to the assessed causality to any of the IMPs. No SAE was observed. Date of the data access was November, 26th, 2014.

Table 1: AE related to any IMP of the trial

Pat-ID	Datum erstes Screening	Beh-Arm lt. Randomisation	Rando-Datum	Datum Studienende	lfd. AE-Nr. (DB)	AE Ereignis	AE Startdatum	AE Enddatum	AE Severity	Outcome	AE-Kausalzus-hg. mit Silibinin	AE-Kausalzus-hg. mit Telaprevir	AE-Kausalzus-hg. mit Ribavirin	AE-Kausalzus-hg. mit Peginterferon	Seriousness
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	5	Schüttelfrost	20.01.2014	20.01.2014	Moderate	Recovered/ Resolved	n. mgl.	n. mgl.	n. mgl.	möglich	No
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	6	Kopfschmerzen	20.01.2014	20.01.2014	Moderate	Recovered/ Resolved	n. mgl.	n. mgl.	n. mgl.	möglich	No
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	7	Schlafstörungen	24.01.2014	.	Mild	no data	n. mgl.	n. mgl.	n. mgl.	möglich	no data
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	9	Juckreiz am After	27.01.2014	27.01.2014	Mild	no data	n. mgl.	möglich	n. mgl.	n. mgl.	No
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	10	Juckreiz an Injektionsstelle	29.01.2014	31.01.2014	Mild	Recovered/ Resolved	n. mgl.	n. mgl.	n. mgl.	möglich	No
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	11	Rötung an Injektionsstelle	29.01.2014	.	.	no data	n. mgl.	n. mgl.	n. mgl.	möglich	No

Anzahl AEs: 6

Table 2: AE unrelated to any IMP of the trial

Pat-ID	Datum erstes Screening	Beh-Arm lt. Randomisation	Rando-Datum	Datum Studienende	lfd. AE-Nr. (DB)	AE Ereignis	AE Startdate	AE Enddate	AE Severity (Code)	Outcome (Code)
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	1	Blähungen	01.01.2014	.	Mild	no information
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	2	trockene Nasenschleimhaut	11.01.2014	.	Mild	no information
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	3	Erkältung	11.01.2014	13609382400	Mild	Recovered/ Resolved
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	4	Juckreiz Rücken	01.12.2014	.	Mild	no information
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	8	Reflux	26.01.2014	13610073600	Mild	Recovered/ Resolved
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	12	Kopfschmerz	01.02.2014	13610592000	Moderate	Recovered/ Resolved
0026	12.12.2014	ArmB (ggf. Resue-Beh.)	09.01.2014	03.03.2014	13	Übelkeit	30.01.2014	13610419200	Mild	Recovered/ Resolved

Anzahl AEs: 7

20.3 Conclusion

Based on only one included patient no conclusions can be drawn regarding the efficacy and safety of a Silibinin treatment added to triple therapy of Telaprevir and Peg/Riba from the HISTORY trial which reach beyond the already known.

21 Date of Report

03.12.2014

22 Appendix

22.1 Table of investigators and study centers

PZ-ID	Adresse	Anrede	Titel	Vorname	Nachname	Funktion
01	Leber- und Studienzentrum am Checkpoint Charlottenstraße 81 **10969 Berlin**	Herr	Dr. med.	Michael	Biermer	Coordinating Investigator/ Investigator
		Herr	Prof. Dr. med.	Thomas	Berg	Deputy Investigator
02	Universitätsklinikum Leipzig - Sektion Hepatologie Klinik u. Poliklinik für Gastroenterologie u. Rheumatologie Haus 4 Liebigstraße 20 **04103 Leipzig**	Herr	Prof. Dr. med.	Thomas	Berg	Investigator
		Herr	PD Dr. med.	Johannes	Wiegand	Deputy Investigator
03	Universitätsklinikum Tübingen Medizinische Klinik Abteilung I Otfried-Müller-Str. 10 **72076 Tübingen**	Herr	Dr. med.	Christoph	Berg	Investigator
		Herr	Dr. med.	Daniel	Egetemeyr	Deputy Investigator
04	Klinikum der J.W. Goethe-Universität Medizinische Klinik 1 Haus 11/ 3 O.G. Theodor-Stern-Kai 7 **60590 Frankfurt am Main**	Herr	Prof. Dr. med.	Stefan	Zeuzem	Investigator
		Frau	Dr. med.	Tanja	Welzel	Deputy Investigator
05	Universitätsklinikum Heidelberg Medizinische Klinik Abt. IV Gastroenterologie/ Hepatologie Im Neuenheimer Feld 410 **69120 Heidelberg**	Herr		Christoph	Eisenbach	Investigator

		Herr	PD Dr. med.	Ronald	Koschny	Deputy Investigator
06	UNIKLINIK KÖLN Klinik f. Gastroenterologie u. Hepatologie am Abdominalzentrum Studienambulanz/ Bettenhaus Eb. 01/C, R. 330 Kerpener Str. 62 **50937 Köln**	Herr	Prof. Dr. med.	Tobias	Goeser	Investigator
		Herr	OA Dr. med.	Dirk	Waldschmidt	Deputy Investigator
07	Universitätsklinikum Regensburg Klinik für Innere Medizin I Abt. f. Gastroenterologie, Endokrinologie, Rheumatologie u. Infektionkrankheiten Franz-Josef-Strauß-Allee 11 **93053 Regensburg**	Herr	PD Dr. med.	Kilian	Weigand	Investigator
		Frau	Dr. med.	Sylvia	Brost	Deputy Investigator
08	Universitätsklinikum Essen Klinik für Gastroenterologie und Hepatologie Zentrum für Innere Medizin Hufelandstraße 55 **45122 Essen**	Herr	Prof. Dr. med.	Guido	Gerken	Investigator
		Herr	Dr. med.	Christoph	Jochum	Deputy Investigator

Table 3: investigators and study centers of the HISTORY-trial

22.2 CONSORT Flow Diagram

Not applicable

22.3 References

See trial protocol