Clinical trial results:
Granulocyte colony stimulating factor (G-CSF) to treat acute-on-chronic liver failure: A multicentre randomized Trial

Summary

EudraCT number	2015-002212-32
Trial protocol	DE
Global end of trial date	17 March 2020
Results information	
Result version number	v1 (current)
This version publication date	28 June 2021
First version publication date	28 June 2021
Summary attachment (see zip file)	_GRAFT_Ergebnisbericht_in_Arzneimittelpruefungen_final2.0_2021-04-12 (_GRAFT_Ergebnisbericht_in_Arzneimittelpruefungen_final2.0_2021-04-12.pdf) SAE per Arm (_Graft-EudraCT_SAE-pArm_PT_SOC.pdf) AE per Arm (>8x reported per Term) (_Graft-EudraCT_AE_pArm_8+times-occurred.pdf)

Trial information

Trial identification	
Sponsor protocol code	GRAFT
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02669680
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00011572

Notes:

Sponsors	
Sponsor organisation name	Universität Leipzig
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany,
Public contact	Thomas Berg, Universität Leipzig, thomas.berg@medizin.uni-leipzig.de
Scientific contact	Thomas Berg, Universität Leipzig, thomas.berg@medizin.uni-leipzig.de

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2020
Global end of trial reached?	Yes
Global end of trial date	17 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

From the clinical point of view, overall survival and transplant-free survival are the most relevant outcome measures. Thus, the primary endpoint of the study is transplant-free survival up to 90 days, with death and liver transplantation (OLT) counting as event

Protection of trial subjects:

For the analysis of clinical endpoints, blood samples were taken and other diagnostic procedures were performed, all standardized according to the current position papers and guidelines. These were generally consistent with the routine treatment of these patients - except for the intervention with G-CSF in the experimental arm.

Background therapy:

n.a.

Evidence for comparator:

n.a.

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 176
Worldwide total number of subjects	176
EEA total number of subjects	176

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	176
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in: 01. March 2016
Last patient in: 04. April 2019
Last patient out: 17. March 2020

Pre-assignment

Screening details:

The aim was to include a total number of 262 patients with evaluable data with regard to the primary and secondary endpoints after intervention with G-CSF or only standard care. To obtain reliable information, 292 patients were planned to be screened and randomized.

Pre-assignment period milestones

Number of subjects started	176
Number of subjects completed	176

Period 1

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

Blinding implementation details:

n.a.

Arms

Are arms mutually exclusive?	Yes
Arm title	G-CSF+SMT

Arm description:

Application of G-CSF (Filgrastim) in combination with standard care of acute-on-chronic liver failure
G-CSF subcutaneously, on day 0-4, then every 3rd day over 26 days (days 7, 10, 13, 16, 19, 22, 25) = 12 doses

Arm type	Experimental
Investigational medicinal product name	G-CSF
Investigational medicinal product code	n.a.
Other name	Filgrastim
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

G-CSF subcutaneously, on day 0-4, then every 3rd day over 26 days (days 7, 10, 13, 16, 19, 22, 25) = 12 doses
G-CSF doses should be guided by the body weight using a cut off value of 70 kg (≤ 70kg 30 Mio IU G-CSF, > 70 kg 48 Mio IU G-CSF)

Arm title	SMT=control

Arm description:

Standard medical treatment/care of acute-on-chronic liver failure

Arm type	control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	G-CSF+SMT	SMT=control
Started	88	88
Completed	88	88

Baseline characteristics

Reporting groups	
Reporting group title	G-CSF+SMT
Reporting group description:	
Application of G-CSF (Filgrastim) in combination with standard care of acute-on-chronic liver failure G-CSF subcutaneously, on day 0-4, then every 3rd day over 26 days (days 7, 10, 13, 16, 19, 22, 25) = 12 doses	

Reporting group title	SMT=control
Reporting group description:	
Standard medical treatment/care of acute-on-chronic liver failure	

Reporting group values	G-CSF+SMT	SMT=control	Total
Number of subjects	88	88	176
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at trial inclusion			
Units: years			
arithmetic mean	54.4	57.1	
standard deviation	± 10.2	± 9.6	-
Gender categorical Units: Subjects			
Female	38	27	65
Male	50	61	111
ACLF grade at inclusion Units: Subjects			
grade 1	39	45	84
grade 2	37	28	65
grade 3	12	15	27
Ascites Units: Subjects			
yes	85	85	170
no	2	3	5
unknown	1	0	1
hepatic encephalopathy			
HE at inclusion			
Units: Subjects			

no	32	26	58
unknown	1	1	2
yes	55	61	116
number of organ failures			
Units: count			
arithmetic mean	1.7	1.4	
standard deviation	± 0.7	± 0.6	-
CLIF-C OF score			
Units: count			
arithmetic mean	10.4	10.3	
standard deviation	± 1.9	± 2.0	-
MELD score			
Units: count			
arithmetic mean	24.4	24.5	
standard deviation	± 6.3	± 6.1	-
CLIF-C ACLF score			
Units: count			
arithmetic mean	51.9	51.2	
standard deviation	± 8.7	± 7.4	-
BMI			
Units: kg/m²			
arithmetic mean	28.9	28.8	
standard deviation	± 4.8	± 5.6	-
MAP			
Units: mm Hg			
arithmetic mean	79.9	82.7	
standard deviation	± 12.0	± 13.2	-
bilirubin			
Units: mg/dl			
arithmetic mean	18.0	18.9	
standard deviation	± 12.0	± 14.5	-
creatinine			
Units: mg/dl			
arithmetic mean	2.4	2.4	
standard deviation	± 1.6	± 1.5	-
INR			
Units: ratio			
arithmetic mean	2.2	2.1	
standard deviation	± 0.8	± 1.0	-
WBC			
Units: Gpt/l			
arithmetic mean	14.8	11.2	
standard deviation	± 12.4	± 7.1	-

End points

End points reporting groups

Reporting group title	G-CSF+SMT
Reporting group description:	
Application of G-CSF (Filgrastim) in combination with standard care of acute-on-chronic liver failure G-CSF subcutaneously, on day 0-4, then every 3rd day over 26 days (days 7, 10, 13, 16, 19, 22, 25) = 12 doses	

Reporting group title	SMT=control
Reporting group description:	
Standard medical treatment/care of acute-on-chronic liver failure	

Primary: transplant-free survival at Day 90/ visit 6

End point title	transplant-free survival at Day 90/ visit 6
End point description:	
either OLT or death = event	
End point type	Primary
End point timeframe:	
Day 90 = visit 6	

End point values	G-CSF+SMT	SMT=control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[1]	88[2]		
Units: subjests				
event occurred	54	51		
censored	34	37		

Notes:

[1] - = Full analysis population

[2] - = Fullanalysis population

Statistical analyses

Statistical analysis title	confirmatory
Comparison groups	G-CSF+SMT v SMT=control
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.805
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.711
upper limit	1.551

Notes:
[3] - Cox regression model

Secondary: overall survival

End point title	overall survival

End point description:

End point type	Secondary

End point timeframe:
Day 360 = visit 8 = end of study

End point values	G-CSF+SMT	SMT=control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: subjects				
death occurred	58	55		
censored	30	33		

Statistical analyses

Statistical analysis title	secondary
Comparison groups	G-CSF+SMT v SMT=control
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	1.541

Secondary: transplant-free survival at Day 360 =End of Study

End point title	transplant-free survival at Day 360 =End of Study

End point description:

End point type	Secondary

End point timeframe:

Day 360 = End of study

End point values	G-CSF+SMT	SMT=control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: Subjects				
event occurred	62	61		
censored	26	27		

Statistical analyses

Statistical analysis title	secondary
Comparison groups	G-CSF+SMT v SMT=control
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.43

Statistical analysis title	secondary
Comparison groups	SMT=control v G-CSF+SMT
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.998

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.43

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Until Day 28; only in case of new malignancies until Day360 but no one was reported	
Adverse event reporting additional description:	
A selection of SAE with fatal outcomes and SAR were reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	GCSF+SMT
Reporting group description:	
GCSF + standard medical treatment	
Reporting group title	SMT=control
Reporting group description:	
standard medical treatment	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: In total, 757 AE were reported with 403 in 80 patients of the G-CSF arm and 354 in 78 Patients of the SMT control arm.
All AE (k=338, with) with frequncies of (at least) 8 occurrences per MedDRA Preferred term were provided per arm in a PDF-File attachted.

Serious adverse events	GCSF+SMT	SMT=control	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 88 (61.36%)	47 / 88 (53.41%)	
number of deaths (all causes)	58	55	
number of deaths resulting from adverse events	37	36	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 88 (1.14%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypotension			
subjects affected / exposed	2 / 88 (2.27%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 88 (0.00%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	

Surgical and medical procedures			
Resuscitation			
subjects affected / exposed	2 / 88 (2.27%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endotracheal intubation			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	11 / 88 (12.50%)	9 / 88 (10.23%)	
occurrences causally related to treatment / all	2 / 11	0 / 9	
deaths causally related to treatment / all	2 / 10	0 / 9	
Ulcer haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 88 (3.41%)	6 / 88 (6.82%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	1 / 3	0 / 2	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asphyxia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			

subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	5 / 88 (5.68%)	10 / 88 (11.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cerebral haemorrhage			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coma hepatic			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Coagulopathy			

subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 88 (5.68%)	4 / 88 (4.55%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Ileus			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal ischaemia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal varices haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal varices haemorrhage			
subjects affected / exposed	2 / 88 (2.27%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatobiliary disorders			

Acute on chronic liver failure			
subjects affected / exposed	8 / 88 (9.09%)	7 / 88 (7.95%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 8	0 / 7	
Hepatic cirrhosis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic failure			
subjects affected / exposed	5 / 88 (5.68%)	6 / 88 (6.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 6	
Hepatorenal syndrome			
subjects affected / exposed	6 / 88 (6.82%)	6 / 88 (6.82%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	2 / 88 (2.27%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Renal failure			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Peritonitis bacterial			
subjects affected / exposed	1 / 88 (1.14%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 3	

Pneumonia			
subjects affected / exposed	1 / 88 (1.14%)	4 / 88 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	3 / 88 (3.41%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Septic shock			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urosepsis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection			
subjects affected / exposed	0 / 88 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	GCSF+SMT	SMT=control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)	0 / 88 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	changes in exclusion criteria, baseline assessments and documentation and reporting of AE/SAE
29 November 2016	addition of new trial sites, change of coordinating investigator
27 July 2018	changes in documentation and reporting of AE/SAE because of new safety information, addition of a new trial site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

n.a.

Notes: