Clinical trial results:
An interventional, single arm, multicenter, phase I/IIa clinical trial to investigate the efficacy and safety of allo-APZ2-ACLF for the treatment of acute-on-chronic liver failure (ACLF)

Summary

EudraCT number	2018-001240-61
Trial protocol	DE AT
Global end of trial date	26 March 2021

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	allo-APZ2-ACLF-II-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03860155
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RHEACELL GmbH & Co. KG
Sponsor organisation address	Im Neuenheimer Feld 517, Heidelberg, Germany, 69120
Public contact	Information Office, RHEACELL GmbH & Co. KG, +49 6221718330, office@rheacell.com
Scientific contact	Information Office, RHEACELL GmbH & Co. KG, +49 6221718330, office@rheacell.com

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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this clinical trial is to investigate the efficacy (by changes in Model for End-Stage Liver Disease [MELD] score) and safety (by monitoring adverse events [AEs]) of 3 doses of allo-APZ2-ACLF administered intravenously to subjects suffering from ACLF.

Protection of trial subjects:

Safety data were continuously reviewed by the medical monitor, with assistance from the coordinating investigator and the sponsor’s medical officer as needed, or a data safety monitoring board (DSMB) established with protocol version 04 from 06-Aug-2019. During the trial, the DSMB was renamed to data monitoring committee (DMC) and consisted of the medical monitor, sponsor's responsible medical officer, the respective representative of the clinical trial center, and an independent expert. The first 6 subjects were planned to be consecutively enrolled under safety and related data review by the DMC. To detect immediate severe adverse effects (eg, allergic reaction, systemic inflammatory response syndrome), the next subject can only be enrolled after the second infusion of the prior subject was considered to be safe by the DMC. A favourable DMC decision report on safety in this subject cohort was required before recruitment of further subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Men and women aged 20 to 75 years with ACLF of grade 2 or 3 as defined by the European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) who were not eligable for liver transplantion were recruited in 4 centers in Germany. The first subject signed the informed consent form (ICF) on 22-Mar-2019 and was a screening failure.

Pre-assignment

Screening details:

In the trial, subjects were enrolled and studied under protocol versions V02 (07-Jan-2019) or V07 (13 May-2020). 5 subjects signed the ICF. 2 subjects were screening failures and not treated with allo-ALZ2-ACLF. 3 subjects were planned to be treated with allo-APZ2-ACLF (2 x 10E6 cells/kg) 3 times within 2 weeks.

Period 1

Period 1 title	Overall treatment until death (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	allo-APZ2-ACLF

Arm description:

Subjects were to receive 3 doses of allo-APZ2-ACLF intravenously within 2 weeks and were to be followed up 24 weeks for efficacy and 24 months for safety after first allo-APZ2-ACLF application.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-ACLF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 3 doses of allo-APZ2-ACLF within 2 weeks (subjects treated according to protocol V02: at Days 0, 4, and 11; subjects treated according to protocol V07: at Days 0, 5, and 13) at least 3 hours after end of dialysis, if applicable. allo-APZ2-ACLF contained allogeneic skin-derived ABCB5-positive mesenchymal stem cells in Human Serum Albumin/Ringer-Lactate/Glucose solution (1 x 10E7 cells/mL) isolated from skin tissue of healthy donors. A dose of 2 x 10E6 cells/kg was given intravenously into the peripheral vein (arm) by use of a perfusor (protocol V02) or with a flow rate of 1-2 mL/min (protocol V07). To prevent allergic reactions, treatment with an antihistamine was mandatory before allo-APZ2-ACLF administration; the type of antihistamine was chosen at the discretion of the investigator.

Number of subjects in period 1	allo-APZ2-ACLF
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	allo-APZ2-ACLF
Reporting group description:	
Subjects were to receive 3 doses of allo-APZ2-ACLF intravenously within 2 weeks and were to be followed up 24 weeks for efficacy and 24 months for safety after first allo-APZ2-ACLF application.	

Reporting group values	allo-APZ2-ACLF	Total	
Number of subjects	3	3	
Age categorical			
Units: Subjects			
Adults (18-64 years)	3	3	
Age continuous			
Units: years			
median	43		
full range (min-max)	34 to 54	-	
Gender categorical			
Units: Subjects			
Female	1	1	
Male	2	2	
Body mass index			
Units: kilogram(s)/square meter			
median	29.4		
full range (min-max)	24.5 to 34.3	-	
Model for End-Stage Liver Disease (MELD) score			
Units: score(s)			
median	41		
full range (min-max)	37 to 43	-	

End points

End points reporting groups

Reporting group title	allo-APZ2-ACLF

Reporting group description:

Subjects were to receive 3 doses of allo-APZ2-ACLF intravenously within 2 weeks and were to be followed up 24 weeks for efficacy and 24 months for safety after first allo-APZ2-ACLF application.

Primary: Safety endpoint adverse events

End point title	Safety endpoint adverse events[1]

End point description:

The primary safety endpoint was the number of subjects with adverse events (AEs). Treatment-emergent adverse events (TEAEs) included all AEs reported from first allo-APZ2-ACLF treatment. Related TEAEs included all TEAEs with a suspected relationship to allo-APZ2-ACLF.

End point type	Primary

End point timeframe:

From Screening until the end of trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this primary end point.

End point values	allo-APZ2-ACLF			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subject(s)				
All AEs	3			
TEAEs	3			
allo-APZ2-ACLF related TEAEs	1			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy endpoint change of MELD score at Week 24

End point title	Efficacy endpoint change of MELD score at Week 24[2]

End point description:

The primary efficacy was the change from Baseline (Day 0) in MELD score at Week 24 or the last available post-baseline measurement if the Week 24 score is missing (last observation carried forward).

End point type	Primary

End point timeframe:

From Baseline (Day 0, before first allo-APZ2-ACLF treatment) to Week 24.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this primary end point.

End point values	allo-APZ2-ACLF			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: score(s)				
arithmetic mean (full range (min-max))	(to)			

Notes:

[3] - All subjects discontinued the trial prematurely, at the latest in Week 4.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening until the end of trial.

Adverse event reporting additional description:

All (3) treated subjects died before trial completion (on Day 5, in Week 3, and in Week 4, respectively) due to a TEAE (deterioration of ACLF, hypotension, and septic shock, respectively) which was not considered related to the IMP by the investigator and the medical monitor.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	allo-APZ2-ACLF

Reporting group description:

Subjects received 3 doses of allo-APZ2-ACLF intravenously within 2 weeks and were followed up 24 weeks for efficacy and 24 months for safety after first allo-APZ2-ACLF application.

Serious adverse events	allo-APZ2-ACLF		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute on chronic liver failure			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal			

disorders			
Respiratory failure	Additional description: The SAE was reported before the first IMP treatment.		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	allo-APZ2-ACLF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Inflammatory marker increased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Polyneuropathy			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
General disorders and administration site conditions Catheter site haemorrhage subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Haematochezia subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Delirium subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Infections and infestations			

Pneumonia subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2020	Subjects were screened and enrolled under protocol versions V02 (07-Jan-2019) or V07 (13-May-2020). Protocol changes to version 02 (07-Jan-2019) were: - treatment schedule of the investigational medicinal product changed from 'at Days 0, 4, and 11' to at 'Days 0, 5 (±1 day), and 13 (±1 day)' - mandatory use of antihistamine (type at the discretion of the investigator) before IMP administration to avoid allergic reactions - continuous monitoring of safety and related data by a DMC consisting of the medical monitor, sponsors' responsible medical officer, and the respective representative of the clinical trial center, rather than safety monitoring by the medical monitor only (in assistance of coordinating investigator and sponsor's medical officer, if necessary) - change in stage-up design of enrollment and treatment of subjects: For the first 6 subjects, the next patient was to be enrolled only after the previous subject's second infusion had been considered safe by the DMC. A safety evaluation in form of the DMC decision report planned after enrollment of 6 subjects to be submitted to the PEI for approval of further subject recruitment. - any death should not lead to a stop of the clinical trial and an evaluation of safety after risk assessment, but to an immediate stop of treatment of all subjects and a stop of enrollment. Safety had to be discussed on a case-by-case basis in the DMC meeting. All grade 3 or 4 AEs considered related to the IMP by the investigator and any AE, event, or condition that required treatment or enrollment interruption were to be discussed by the DMC. If considered necessary by the DMC, subject treatment or enrollment were then to be stopped.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 June 2019	One subject died, resulting in stop of the clinical trial for risk assessment according to protovol version 02.	07 October 2019
31 March 2020	Subject recruitment was interrupted due to the COVID-19 pandemic.	05 June 2020
17 September 2020	Two more subjects died. The sponsor decided to terminate the trial prematurely on 26-Mar-2021. The chosen subject population in this trial was complex and characterized by a very high mortality rate (up to 90%), which entailed regular queries and restrictions by the authorities and greatly complicated the conduct of the trial. The scenario may have significantly limited the suitability of the trial design to demonstrate the safety of the investigational medicinal product.	-

Notes:

Limitations and caveats

None reported