Clinical trial results:
A Phase I-IIa trial to assess the safety and antitumor activity of autologous CD44v6 CAR T-cells in acute myeloid leukemia and multiple myeloma expressing CD44v6.

Summary

EudraCT number	2018-000813-19
Trial protocol	CZ IT
Global end of trial date	18 June 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	EURE-CART-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AGC Biologics S.p.A.
Sponsor organisation address	Via Meucci, 3 , Bresso (Milan), Italy, 20091
Public contact	Anna Stornaiuolo, AGC Biologics S.p.A., 0039 0221277440, astornaiuolo@agcbio.com
Scientific contact	Anna Stornaiuolo, AGC Biologics S.p.A., 0039 0221277440, astornaiuolo@agcbio.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	07 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objectives of Phase I
1. To determine the maximum tolerated dose (MTD) and recommended phase IIa dose of MLMCAR44.1 T-cells in patients with relapsed/refractory acute myeloid leukemia (AML) or multiple myeloma (MM) expressing CD44v6.
2. To evaluate the overall safety of treatment with MLM-CAR44.1 T-cells.
3. To monitor for the absence of replication-competent retrovirus (RCR)

Primary objective of phase IIa
To evaluate hematological response to MLM-CAR44.1 T-cells in AML and MM.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study was performed in compliance with Good Clinical Practices (CPMP/ICH/135/95), and the essential documents are archived as required by the applicable regulatory requirements. The study and any amendments were reviewed by an Independent Ethics Committees or Institutional Review Boards.

Background therapy:

All patients were pre-treated with Proteasome inhibitor, high-dose alkylating agent, IMID, monoclonal antibodies from 2 up to 3 lines of treatment.

Evidence for comparator: -

Actual start date of recruitment	27 August 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	7
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The multicenter study was conducted at 3 Institutions:
-Coordinating Center: Haematology and Bone Marrow Transplant Unit, Ospedale San Raffaele, Milan, Italy;
-Paediatric Haematology and Oncology Unit, Ospedale Pediatrico Bambino Gesù, Rome, Italy;
-Department of Haematooncology, Fakultni Nemocnice, Czech Republic.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	8
Number of subjects completed	8

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	MLM-CAR44.1 T-cells Infusion

Arm description:

Patients were scheduled to receive a single intravenous (iv) infusion of CD44v6.CAR-transduced autologous
lymphocytes at day 0, after lymphodepleting chemotherapy with cyclophosphamide iv (500 mg/m2) and fludarabine iv (30 mg/m2) performed daily from day -5 to day -3

The dose of iv infused MLM-CAR44.1 T-cells is:

PHASE I: 0.5x10E6/Kg or 1x10E6/Kg or 2x10E6/Kg according to the BOIN design. PHASE IIa: a dose of MLMCAR44.1 T-cells corresponding to the maximum tolerated dose (MTD).

Arm type	Experimental
Investigational medicinal product name	MLM-CAR44.1 T-cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were scheduled to receive a single intravenous (iv) infusion of CD44v6.CAR-transduced autologous
lymphocytes at day 0, after lymphodepleting chemotherapy with cyclophosphamide iv (500 mg/m2) and fludarabine iv (30 mg/m2) performed daily from day -5 to day -3

PHASE I: 0.5x10E6/Kg or 1x10E6/Kg or 2x10E6/Kg according to the BOIN design. PHASE IIa: a dose of MLMCAR44.1 T-cells corresponding to the maximum tolerated dose (MTD).

Number of subjects in period 1	MLM-CAR44.1 T-cells Infusion
Started	8
Completed	2
Not completed	6
Disease progression	1
Screening failures	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	56		
full range (min-max)	41 to 66	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	6	6	
Race (NIH/OMB) Units: Subjects			
White	8	8	
Region of Enrollment Units: Subjects			
Italy	5	5	
Czechia	3	3	
Confirmed diagnosis of MM Units: Subjects			
Confirmed diagnosis of MM	8	8	
Patients with relapse or refractory disease Units: Subjects			
Patients with relapse or refractory disease	8	8	

End points

End points reporting groups

Reporting group title	MLM-CAR44.1 T-cells Infusion

Reporting group description:

Patients were scheduled to receive a single intravenous (iv) infusion of CD44v6.CAR-transduced autologous
lymphocytes at day 0, after lymphodepleting chemotherapy with cyclophosphamide iv (500 mg/m2) and fludarabine iv (30 mg/m2) performed daily from day -5 to day -3

The dose of iv infused MLM-CAR44.1 T-cells is:

PHASE I: 0.5x10E6/Kg or 1x10E6/Kg or 2x10E6/Kg according to the BOIN design. PHASE IIa: a dose of MLMCAR44.1 T-cells corresponding to the maximum tolerated dose (MTD).

Primary: Phase I: Maximum Tolerated Dose (MTD) and the Recommended Phase IIa Dose of MLM-CAR44.1 T-cells in AML and MM

End point title	Phase I: Maximum Tolerated Dose (MTD) and the Recommended Phase IIa Dose of MLM-CAR44.1 T-cells in AML and MM[1]

End point description:

MTD established through BOIN design and the dose-limiting toxicities (DLTs) occurring following CAR T-cell infusion.

End point type	Primary

End point timeframe:

Within 30 days following CAR T-cell infusion, assessed as day 0

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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Overall Number of Participants Analyzed				

Notes:

[2] - Data were not collected due to early end of trial

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Overall Safety of Treatment With MLM-CAR44.1 T-cells

End point title	Phase I: Overall Safety of Treatment With MLM-CAR44.1 T-

End point description:

Safety will be evaluated by analyzing the type, frequency and severity of adverse events (AE) and by monitoring for
systemic reactions (fever, tachycardia, nausea and vomiting, joint pain, skin rash).

Overall, 3 study emergent serious adverse events (SAEs) were reported in patients treated with MLM-CAR44.1 T-cells.

End point type	Primary

End point timeframe:

For 30 days following CAR T-cell infusion, assessed as day 0.

Notes:

[3] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of SAEs	3			

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 3 Months Post-infusion

End point title	Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 3 Months Post-infusion[4]

End point description:

The absence of replication competent retrovirus (RCR) in blood specimens: 3 months post-infusion will be monitored by DNA PCR for the Galv gene.
RCR search was conducted centrally using a quantitative molecular test, (real time quantitative PCR, q-PCR analysis) determining the absence of RCR by DNA PCR for the Galv and gag-pol genes on genomic DNA from patient's peripheral blood lymphocytes. The objective of this q-PCR analysis is to exclude the presence of RCR originated by recombination with PG13 packaging cell sequences by detecting the Galv and gag-pol transcripts in the transduced cells. The absence of the Galv and gag-pol transcripts can exclude the presence of an RCR, while its presence is not sufficient to indicate the presence of an RCR, and in this case further analysis is required.

End point type	Primary

End point timeframe:

3 months after infusion (assessed as day 0)

Notes:

[4] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Count of Participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 6 Months Post-infusion

End point title	Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 6 Months Post-infusion[5]

End point description:

The absence of replication competent retrovirus (RCR) in blood specimens will be monitored by DNA PCR for the Galv gene.
RCR search was conducted centrally using a quantitative molecular test, (real time quantitative PCR, q-PCR analysis) determining the absence of RCR by DNA PCR for the Galv and gag-pol genes on genomic DNA from patient's peripheral blood lymphocytes. The objective of this q-PCR analysis is to exclude the presence of RCR originated by recombination with PG13 packaging cell sequences by detecting the Galv and gag-pol transcripts in the transduced cells. The absence of the Galv and gag-pol transcripts can exclude the presence of an RCR, while its presence is not sufficient to indicate the presence of an RCR, and in this case further analysis is required

End point type	Primary

End point timeframe:

6 months after infusion (assessed as day 0)

Notes:

[5] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Count of Participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 12 Months Post-infusion

End point title	Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 12 Months Post-infusion[6]

End point description:

The absence of replication competent retrovirus (RCR) in blood specimens will be monitored by DNA PCR for the Galv gene.

End point type	Primary

End point timeframe:

12 months after infusion (assessed as day 0)

Notes:

[6] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: Overall Number of Participants Analyzed				

Notes:

[7] - Data were not collected due to early end of trial

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 24 Months Post-infusion

End point title	Phase I: Absence of Replication Competent Retrovirus (RCR) in Blood Specimens: 24 Months Post-infusion[8]

End point description:

The absence of replication competent retrovirus (RCR) in blood specimens will be monitored by DNA PCR for the Galv gene

End point type	Primary

End point timeframe:

24 months after infusion (assessed as day 0)

Notes:

[8] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: Overall Number of Participants Analyzed				

Notes:

[9] - Data were not collected due to early end of trial

Statistical analyses

No statistical analyses for this end point

Primary: Phase IIa: Hematological Disease Response to MLM-CAR44.1 T-cells in AML

End point title	Phase IIa: Hematological Disease Response to MLM-CAR44.1 T-cells in AML[10]

End point description:

The hematologic disease response will be classified according to ELN criteria

End point type	Primary

End point timeframe:

2 months after MLM-CAR44.1 T-cell infusion, assessed as day 0

Notes:

[10] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: Overall Number of Participants Analyzed				

Notes:

[11] - Data were not collected because Phase IIa was not performed due to early end of trial

Statistical analyses

No statistical analyses for this end point

Primary: Phase IIa: Hematological Disease Response to MLM-CAR44.1 T-cells in MM

End point title	Phase IIa: Hematological Disease Response to MLM-CAR44.1 T-cells in MM[12]

End point description:

The hematologic disease response will be classified according to IMWG criteria

End point type	Primary

End point timeframe:

3 months after T-cell infusion, assessed as day 0

Notes:

[12] - 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: Due to the low number of enrolled and treated patients no statistical analysis were performed.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2[13]			
Units: Count of Participants	0			

Notes:

[13] - Data were not collected because Phase IIa was not performed due to early end of trial

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Hematologic Disease Response to MLM-CAR44.1 T-cells in AML

End point title	Phase I: Hematologic Disease Response to MLM-CAR44.1 T-cells in AML

End point description:

The hematologic disease response will be classified with the following response criteria: complete response (CR), incomplete response (CRi) and partial response (PR) according to ELN criteria.

End point type	Secondary

End point timeframe:

1 and 2 months following T-cell infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: Overall Number of Participants Analyzed				

Notes:

[14] - Data were not collected because no AML patients were enrolled

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: Hematologic Disease Response to MLM-CAR44.1 T-cells in MM

End point title	Phase I: Hematologic Disease Response to MLM-CAR44.1 T-cells in MM

End point description:

Hematologic disease response evaluated at Day 28 following CART-cell infusion, as overall response rate (ORR), stringent complete response (sCR), CR, very good partial response (VGPR) and partial response (PR).

End point type	Secondary

End point timeframe:

1 and 3 months following T-cell infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Count of Participants				
No response detected	2			
Hematologic disease response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: The Levels of Circulating MLM-CAR44.1 T-cells in Blood Samples

End point title	Phase I: The Levels of Circulating MLM-CAR44.1 T-cells in Blood Samples

End point description:

The levels will be evaluated by flow cytometry and qPCR (in vivo pharmacokinetic profile).

End point type	Secondary

End point timeframe:

At day 7, 14, 21, 28, 60, 90, 180 from infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Count of Participants				
Positive at day 14 and 21	1			
Negative at all monitoring time points	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I: The Percentage of Patients for Whom Activation of Suicide Gene Was Needed

End point title	Phase I: The Percentage of Patients for Whom Activation of Suicide Gene Was Needed

End point description:

Suicide gene activation and elimination of transduced cells will be established through administration of ganciclovir in case of cytokine-release syndrome (CRS) and other MLM-CAR44.1 T-cell related toxicities.

End point type	Secondary

End point timeframe:

At day 7, 14, 21, 28, 60, 90, 180 from infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: Overall Number of Participants Analyzed				

Notes:

[15] - Data were not collected because no MLM-CAR44.1 T-cell related toxicities occurred

Statistical analyses

No statistical analyses for this end point

Secondary: Phase IIa: Hematologic Disease Response in AML

End point title	Phase IIa: Hematologic Disease Response in AML

End point description:

The hematologic disease response will be classified with the following response criteria: complete response (CR), incomplete response (CRi) and partial response (PR) according to ELN criteria.

End point type	Secondary

End point timeframe:

1, 2 and 6 months after MLM-CAR44.1 T-cell infusion, assessed as day 0.

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: Overall Number of Participants Analyzed				

Notes:

[16] - Data were not collected because Phase IIa was not performed due to early end of trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase IIa: Hematologic Disease Response in MM

End point title	Phase IIa: Hematologic Disease Response in MM

End point description:

The hematologic disease response will be defined based on the overall response rate (ORR): stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) according to IMWG criteria

End point type	Secondary

End point timeframe:

1, 2 and 6 months after T-cell infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: Overall Number of Participants Analyzed				

Notes:

[17] - Data were not collected because Phase IIa was not performed due to early end of trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase IIa: Overall Survival (OS)

End point title	Phase IIa: Overall Survival (OS)

End point description:

Overall Survival (OS) is defined as the time from the date of MLM-CAR44.1 T-cell infusion to the date of last follow-up or death due to any cause, whichever occurs first. One patients out of the 2 treated was still alive at the date of the early study termination. One patient died after EURE-CART-1 cell infusion, at

day 121, for disease progression.

End point type	Secondary

End point timeframe:

At the date of the early study termination

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: Overall Number of Participants Analyzed				

Notes:

[18] - Data were not collected because Phase IIa was not performed due to early end of trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Exploratory Outcome of Phase IIa: Percentages of Patients With Minimal Residual Disease

End point title	Exploratory Outcome of Phase IIa: Percentages of Patients With Minimal Residual Disease

End point description:

AML: proportion of patients with a molecular complete response (CR); MM: proportion of patients with a molecular CR.

End point type	Secondary

End point timeframe:

AML: 2 months after infusion, assessed as day 0. MM: 3 months after infusion, assessed as day 0

End point values	MLM-CAR44.1 T-cells Infusion			
Subject group type	Reporting group			
Number of subjects analysed	0[19]			
Units: Overall Number of Participants Analyzed				

Notes:

[19] - Data were not collected because Phase IIa was not performed due to early end of trial.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed up to 15 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	MLM-CAR44.1 T-cells Infusion

Reporting group description:

Patients were scheduled to receive a single intravenous (iv) infusion of CD44v6.CAR-transduced autologous
lymphocytes at day 0, after lymphodepleting chemotherapy with cyclophosphamide iv (500 mg/m2) and fludarabine iv (30 mg/m2) performed daily from day -5 to day -3

The dose of iv infused MLM-CAR44.1 T-cells is:

PHASE I: 0.5x10E6/Kg or 1x10E6/Kg or 2x10E6/Kg according to the BOIN design. PHASE IIa: a dose of MLMCAR44.1 T-cells corresponding to the maximum tolerated dose (MTD).

Serious adverse events	MLM-CAR44.1 T-cells Infusion		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	MLM-CAR44.1 T-cells Infusion		
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 2 (100.00%)		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 2		
Neutropenia subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 2		
Immune system disorders Pyrexia subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2020	Clinical Study Protocol, version C

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 June 2021	The early termination of this study is due to the analysis of its feasibility, based on the low patient recruitment rate (due to the lower-than-expected proportion of myeloma and leukemia expressing the CD44v6). A further decrease in the recruitment occurred with the diffusion of the COVID-19 emergency and the availability of new drugs for the treatment of myeloma and leukemia. These reasons make impossible to foresee the conclusion of the study in a clinically relevant time frame.	-

Notes:

Limitations and caveats

None reported