



## Clinical trial results: Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation Study Summary

EudraCT number	2011-004977-10
Trial protocol	DE BG
Global end of trial date	22 February 2019

### Results information

Result version number	v1 (current)
This version publication date	24 July 2022
First version publication date	24 July 2022

### Trial information

#### Trial identification

Sponsor protocol code	08meInnereA_GALACTIC
-----------------------	----------------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00512759
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	University Hospital Basel
Sponsor organisation address	Petersgraben 4, Basel, Switzerland, 4031
Public contact	Principle Investigator, University Hospital Basel, Cardiology, +41 613286549, christian.mueller@usb.ch
Scientific contact	Principle Investigator, University Hospital Basel, Cardiology, 0613286968 613286549, christian.mueller@usb.ch

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 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2019
Global end of trial reached?	Yes
Global end of trial date	22 February 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The aim of the study was to determine the safety and efficacy of an early goal-directed preload and afterload decrement with a target systolic blood pressure of 90-110 mm Hg by aggressive vasodilatation versus standard medical care in a non-ICU setting in patients with acute heart failure.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

AHF therapies other than vasodilators, including diuretics, were provided according to guidelines and at the discretion of the treating physician in both groups. The study protocol defined vasodilator treatment in the intervention group until hospital discharge or day 7 (whichever came first). The ACE-inhibitor (or ARB or sacubitril/valsartan) up-titration until hospital discharge was faster than in the usual care, so patients in the intervention group were expected to receive a significantly higher dose of ACE-inhibitors or ARB or sacubitril/valsartan at the time of discharge.

Evidence for comparator:

-

Actual start date of recruitment	10 December 2007
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	Spain: 4
Country: Number of subjects enrolled	Bulgaria: 58
Country: Number of subjects enrolled	Germany: 50
Country: Number of subjects enrolled	Switzerland: 637
Country: Number of subjects enrolled	Brazil: 39
Worldwide total number of subjects	788
EEA total number of subjects	112

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)	109
From 65 to 84 years	449
85 years and over	230

## Subject disposition

### Recruitment

Recruitment details:

Patients presenting with acute heart failure at the emergency departments at the participating study sites were recruited if they fulfilled all the inclusion and none of the exclusion criteria.

### Pre-assignment

Screening details:

The number of patients assessed for eligibility is not reported because it was not collected at all sites. If the patient fulfilled all the inclusion and none of the exclusion criteria, the patient was randomized. A total of 788 patients were randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	early goal-directed therapy

Arm description:

Early goal-directed therapy applied aggressive vasodilatation using sublingual and transdermal nitrates, hydralazine to avoid tolerance to nitrates, and rapid uptitration of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with a target systolic blood pressure of 90mmHg to 110mmHg. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician

Arm type	Alternative treatment strategy
Investigational medicinal product name	sublingual and transdermal nitrates
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet, Transdermal patch
Routes of administration	Sublingual use, Transdermal use

Dosage and administration details:

Goal-directed preload and afterload decrement strategy through early intensive and sustained vasodilation, was a comprehensive pragmatic approach of maximal and sustained vasodilation combining high and individualized doses of sublingual and transdermal nitrates, oral hydralazine for 48 hours (7–9) and rapid up-titration of ACEinhibitors or ARB or sacubitril/valsartan according to pre-treatment and/or the preference of the treating physician, using a predefined safety corridor for systolic blood pressure of 90-110mmHg.

<b>Arm title</b>	standard of care
------------------	------------------

Arm description:

SoC. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician

Arm type	standard of care
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	early goal-directed therapy	standard of care
Started	386	402
Completed	382	399
Not completed	4	3
Consent withdrawn by subject	1	2
Consent not available at monitoring visit	3	1

## Baseline characteristics

### Reporting groups

Reporting group title	early goal-directed therapy
Reporting group description:	
Early goal-directed therapy applied aggressive vasodilatation using sublingual and transdermal nitrates, hydralazine to avoid tolerance to nitrates, and rapid uptitration of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with a target systolic blood pressure of 90mmHg to 110mmHg. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician	
Reporting group title	standard of care
Reporting group description:	
SoC. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician	

Reporting group values	early goal-directed therapy	standard of care	Total
Number of subjects	386	402	788
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			
Units: years			
median	78.0	77.0	
inter-quartile range (Q1-Q3)	70.0 to 85.0	69.0 to 84.0	-
Gender categorical			
Units: Subjects			
Female	142	149	291
Male	244	253	497
BMI			
Body mass index			
Units: kilogram(s)/square metre			
median	26.5	26.6	
inter-quartile range (Q1-Q3)	23.4 to 30.3	23.5 to 29.7	-
BNP			
brain natriuretic peptide			
Units: nanogram(s)/litre			
median	1249	1272	
inter-quartile range (Q1-Q3)	849 to 2254	845 to 2146	-
NT-proBNP			
N-terminal pro b-type natriuretic peptide			

Units: nanogram(s)/litre			
median	6135	5336	
inter-quartile range (Q1-Q3)	3359 to 9899	3021 to 9517	-
LVEF			
left ventricular ejection fraction			
Units: percent			
median	36	37	
inter-quartile range (Q1-Q3)	26 to 50	26 to 51	-

## End points

### End points reporting groups

Reporting group title	early goal-directed therapy
Reporting group description: Early goal-directed therapy applied aggressive vasodilatation using sublingual and transdermal nitrates, hydralazine to avoid tolerance to nitrates, and rapid uptitration of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with a target systolic blood pressure of 90mmHg to 110mmHg. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician	
Reporting group title	standard of care
Reporting group description: SoC. Timing and dosing of diuretics and all other treatments were left to the discretion of the treating physician	

### Primary: All cause mortality or rehospitalization due to heart failure at 180 days

End point title	All cause mortality or rehospitalization due to heart failure at 180 days
End point description:	
End point type	Primary
End point timeframe: 11-Dec-2007 - 19-Aug-2018	

End point values	early goal-directed therapy	standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	399		
Units: 228	117	111		

### Statistical analyses

Statistical analysis title	All-cause mortality or rehospitalization at 180d
Statistical analysis description: Composite of all-cause mortality or rehospitalization for AHF at 180 days.	
Comparison groups	early goal-directed therapy v standard of care
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Cox
Parameter estimate	Cox proportional hazard



Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.39

### Secondary: All-cause mortality at 180 days

End point title	All-cause mortality at 180 days
End point description:	
End point type	Secondary
End point timeframe:	
11-Dec-2007 - 19-Aug-2018	

End point values	early goal-directed therapy	standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	399		
Units: 116	55	61		

### Statistical analyses

<b>Statistical analysis title</b>	All-cause death at 180 days
Comparison groups	early goal-directed therapy v standard of care
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute difference in percentage
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	6.1

### Secondary: median length of stay

End point title	median length of stay
End point description:	
End point type	Secondary

End point timeframe:  
11-Dec-2007 - 19-Aug-2018

End point values	early goal-directed therapy	standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	399		
Units: days	9	9		

### Statistical analyses

Statistical analysis title	median length of stay
Comparison groups	early goal-directed therapy v standard of care
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Absolute difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

### Secondary: systolic blood pressure on day 2

End point title	systolic blood pressure on day 2
End point description:	
End point type	Secondary
End point timeframe:	
11-Dec-2007 - 20-Feb-2018	

End point values	early goal-directed therapy	standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	399		
Units: mmHG	115	125		

## Statistical analyses

<b>Statistical analysis title</b>	systolic blood pressure on day 2
Comparison groups	early goal-directed therapy v standard of care
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Absolute difference
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	14

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

10-Dec-2007 - 22-Feb-2019

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	SNOMED CT
-----------------	-----------

Dictionary version	1.0
--------------------	-----

### Reporting groups

Reporting group title	early goal-directed therapy
-----------------------	-----------------------------

Reporting group description: -

Reporting group title	standard of care
-----------------------	------------------

Reporting group description: -

Serious adverse events	early goal-directed therapy	standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	199 / 382 (52.09%)	204 / 399 (51.13%)	
number of deaths (all causes)	55	61	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
All-cause rehospitalization			
subjects affected / exposed	167 / 382 (43.72%)	167 / 399 (41.85%)	
occurrences causally related to treatment / all	0 / 167	0 / 167	
deaths causally related to treatment / all	0 / 0	0 / 0	
AHF rehospitalization			
subjects affected / exposed	77 / 382 (20.16%)	70 / 399 (17.54%)	
occurrences causally related to treatment / all	0 / 77	0 / 70	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	55 / 382 (14.40%)	61 / 399 (15.29%)	
occurrences causally related to treatment / all	0 / 55	0 / 61	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolongation of index hospitalization			

subjects affected / exposed	39 / 382 (10.21%)	23 / 399 (5.76%)	
occurrences causally related to treatment / all	0 / 39	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfer to the intensive care unit			
subjects affected / exposed	14 / 382 (3.66%)	16 / 399 (4.01%)	
occurrences causally related to treatment / all	0 / 14	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary resuscitation			
subjects affected / exposed	5 / 382 (1.31%)	4 / 399 (1.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	early goal-directed therapy	standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 382 (60.99%)	197 / 399 (49.37%)	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	5 / 382 (1.31%)	1 / 399 (0.25%)	
occurrences (all)	5	1	
Arrhythmia requiring therapy			
subjects affected / exposed	2 / 382 (0.52%)	3 / 399 (0.75%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Hypokalaemia			
subjects affected / exposed	88 / 382 (23.04%)	98 / 399 (24.56%)	
occurrences (all)	88	98	
Hyperkalaemia			
subjects affected / exposed	41 / 382 (10.73%)	28 / 399 (7.02%)	
occurrences (all)	41	28	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	101 / 382 (26.44%)	38 / 399 (9.52%)	
occurrences (all)	101	38	

Dizziness			
subjects affected / exposed	58 / 382 (15.18%)	39 / 399 (9.77%)	
occurrences (all)	58	39	
Systolic arterial hypotension			
subjects affected / exposed	29 / 382 (7.59%)	9 / 399 (2.26%)	
occurrences (all)	29	9	
Fall			
subjects affected / exposed	14 / 382 (3.66%)	7 / 399 (1.75%)	
occurrences (all)	14	7	
Renal and urinary disorders			
worsening renal function			
subjects affected / exposed	81 / 382 (21.20%)	80 / 399 (20.05%)	
occurrences (all)	81	80	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2007	Eligibility criteria were expanded. Eligible patients should be older than 45 years (instead of 18) to avoid inclusion of possible pregnant women. Exclusion criteria list was expanded. Therapy schema was modified for a better overview
21 April 2008	Primary endpoint "Count of the hospitalization's days after 60 days" was classified as secondary endpoint. The secondary endpoint "Mortality or Hospitalizations after 180 days" is now the primary endpoint of the study. Study population was increased from 351 patients per group to 385 patients per group. Third tone would be assessed using a special holter device (Audicor) during the first 24 hours. At the beginning of the hospitalization and before discharge, lower limbs circumference and central venous pressure will be measured, the latest not invasively using an ultrasound device. At admission, at 48 hours and before discharge, subjective dyspnea assessment will be carried
28 July 2008	The primary endpoint "mortality or hospitalizations after 180 days" was changed to "mortality or rehospitalizations due to heart failure after 180 days". No sample size adjustment. New study centers were included to the discussion for future participation in the study: University Hospital Zürich, Inselspital Bern, Cantonal Hospital in Freiburg and Massachusetts General Hospital in Boston, USA. NT-proBNP was incorporated as alternative inclusion criteria to BNP.
06 October 2008	Additional collection of 7.5ml Urine sample at admission, at 24 and 48 hours, after 6 days and before discharge was included.

21 January 2009	<p>The treatment schema was complemented. In the intervention group, for every medication at every time point, a tolerance margin was established. For standard of care group, the treatment was updated according to the latest recommendations of the European Society of Cardiology (ESC).</p> <p>The approach of special situations (i.e. rise in creatinine, symptomatic hypotony) was stated clearly.</p> <p>Eligible patients should be older than 18 years (instead of 45). To exclude the possibility of enrolling possible pregnant women, a pregnancy test is required.</p> <p>Inclusion of patients that were initially not in the situation to sign the ICF by him/herself, was further clarify in the protocol.</p> <p>Summary was updated.</p>
11 March 2009	<p>Target dose of ACE-i and ARB were adjusted in the control group</p>
07 January 2012	<p>Treatment schema (intervention and standard of care) for ACE-i and ARB was updated with equivalent doses for different substances within the same category.</p> <p>Hospital Clinic of the Faculty of Medicine University of São Paulo Brazil, University Medicine Mainz in Germany and Faculty of Medicine University of Latvia in Riga, Latvia were incorporated in the list of active centers.</p> <p>Biobank regulation V 1.0 was established in accordance with the Swiss Academy of Medical Sciences.</p>
09 January 2013	<p>Acute coronary syndrome and symptomatic hypotension during initial hospitalization were listed as secondary endpoints.</p> <p>Exclusion criteria list was expanded to include: severe mitral stenosis, isolated right ventricular failure due to pulmonary hypertension, Systemic Lupus erythematosus and related diseases and known hypersensitivity to hydralazine or dihydralazine.</p> <p>Study procedures were expanded.</p> <p>Study scheduled was expanded.</p> <p>References were updated.</p>
31 October 2015	<p>The Mafrag Hospital Abu Dhabi (United Arab Emirates), the Hospital Universitari Germans Trias i Pujol in Barcelona Spain, the Hospital de la Santa Creu i Sant Pau in Barcelona Spain and the University Hospital Belgrade (Serbian) were listed as participant centers.</p> <p>Adjustment of the cut-off from NT-proBNP and BNP for eligibility in patients with BMI &gt; 35kg/m<sup>2</sup></p> <p>Treatment schema was updated to include Entresto (LCZ696) up titration plan in the intervention group.</p> <p>Measurements with the Audicor holter device would not take place anymore.</p> <p>Introduction of a "randomization questionnaire" as an assessment tool to measure the influence of the patient due to the open-label study design.</p> <p>Quality of life questionnaire will be only assess at 180 days after inclusion in the study.</p>



26 September 2016	<p>Composite primary endpoint was divided and listed individually as secondary endpoints (allcause mortality at 180 days and HF rehospitalization at 180 days)</p> <p>University Hospital "Tsaritsa Joanna-ISUL" (Sofia, Bulgaria), the National Transport Hospital "Tsar Boris III" (Sofia, Bulgaria), the 5-th Multifunctional Hospital for Active Treatment (Sofia, Bulgaria) and the University Hospital "Alexandrovska" (Sofia, Bulgaria) were listed as participant centers.</p> <p>During the initial phase of treatment in the intervention groups, nitro spray (containing 0.4 mg glyceryl trinitrate per application) can be used as an alternative to nitro capsules.</p> <p>The change from an ACE-i and ARB to LCZ696 is possible at any time by the clinical team, both in the standard group and in the intervention group, as long as the corresponding criteria according to the current 2016 ESC Guidelines are met.</p> <p>SecuTrial (interActive Systems GmbH, Berlin Germany) will be used together with Microsoft Access as the study database.</p> <p>Centers outside Switzerland can organize their own insurance policies.</p>
-------------------	---

Notes:

---

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

---

## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31846016>