Clinical trial results:
GLUTAmate for Metabolic Intervention in Coronary Surgery II

Summary

EudraCT number	2011-006241-15
Trial protocol	SE
Global end of trial date	30 September 2020

Results information

Result version number	v1 (current)
This version publication date	06 June 2024
First version publication date	06 June 2024

Trial information

Trial identification

Sponsor protocol code	GLUTAMICS2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02592824
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Region Östergötland
Sponsor organisation address	Linköping University Hospital, Linköping, Sweden, SE58185
Public contact	Dept Cardiothoracic Surgery, Linköping University Hospital, 46 101034825, rolf.svedjeholm@liu.se
Scientific contact	Dept Cardiothoracic Surgery, Linköping University Hospital, 46 101034825, rolf.svedjeholm@liu.se

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	28 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	Yes
Global end of trial date	30 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim was to confirm that intravenous glutamate infusion reduces the risk of postoperative heart failure in patients undergoing CABG by demonstrating mitigated increase of NT-proBNP, a biomarker for heart failure, postoperatively.

Protection of trial subjects:

The Swedish Patient Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2015
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	Sweden: 314
Worldwide total number of subjects	314
EEA total number of subjects	314

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)	31
From 65 to 84 years	283
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were eligible for the study if they had been accepted for on-pump CABG +/- additional procedure, due to at least two vessel disease or left main stenosis. Moreover, patients had to be at moderate- to high risk of postoperative heart failure because of LVEF <= 0.30 or EuroSCORE >=3.0 with a cardiac or procedure-related risk factor.

Pre-assignment

Screening details:

Screening was done by the clinical investigators at four academic Cardiac Surgery Centers in Sweden.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Patients, staff, and investigators were blinded to the infused treatment (clear transparent solutions). Allocation was concealed until the study was terminated by keeping the randomization codes at APL, Sweden. For safety reasons, the sponsor had access to sealed opaque envelopes to permit intervention to be revealed in cases of SUSAR, mortality, or stroke within 24 hours of surgery. The external monitoring team checked all envelopes at the end of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravenous Glutamate infusion

Arm description:

Intravenous infusion of a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.

Arm type	Experimental
Investigational medicinal product name	L-glutamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Blinded intravenous infusion of either a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After declamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused.

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Blinded intravenous infusion of either a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After declamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused.

Arm title	Intravenous Saline infusion (Placebo)

Arm description:

Intravenous infusion of saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Blinded intravenous infusion of either a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After declamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused.

Number of subjects in period 1	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)
Started	155	159
Completed	148	155
Not completed	7	4
Lost to follow-up	2	1
Exclusion criteria	5	3

Baseline characteristics

Reporting groups

Reporting group title	Intravenous Glutamate infusion

Reporting group description:

Intravenous infusion of a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.

Reporting group title	Intravenous Saline infusion (Placebo)

Reporting group description:

Intravenous infusion of saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.

Reporting group values	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)	Total
Number of subjects	155	159	314
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	11	31
From 65-84 years	135	148	283
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	73	75	
standard deviation	± 7	± 7	-
Gender categorical Units: Subjects			
Female	40	44	84
Male	115	115	230
Preoperative NT-proBNP Units: ng/L			
arithmetic mean	2680	2354	
standard deviation	± 4595	± 3124	-

End points

End points reporting groups

Reporting group title	Intravenous Glutamate infusion
Reporting group description:	
Intravenous infusion of a 0.125M L-glutamic acid solution or saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.	
Reporting group title	Intravenous Saline infusion (Placebo)
Reporting group description:	
Intravenous infusion of saline, at a rate of 1.65 mL/ kg body weight /h. The infusion was started 10-20 min before the anticipated release of the aortic cross-clamp. After unclamping the infusion was continued for another 2 h, then the infusion rate was halved, and an additional 50 mL was infused. The maximum volume infused to any patient was 500 mL of study solution.	

Primary: Postoperative increase of plasma NT-proBNP

End point title	Postoperative increase of plasma NT-proBNP
End point description:	
Plasma NT-proBNP reflects the degree of myocardial dysfunction	
End point type	Primary
End point timeframe:	
Podstoperative increase of plasma NT-proBNP from the preoperative day to postoperative day 3	

End point values	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145[1]	150[2]		
Units: ng/L				
arithmetic mean (standard deviation)	5390 (± 5396)	6452 (± 5215)		

Notes:

[1] - Seven patients excluded. Sampling for NT-proBNP missed in 3 patients on postop day 3

[2] - Four patients excluded. Sampling for BT-proBNP missed in 5 patients on postop day 3.

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
Two-sided Student’s t-test was used. Levene’s test was used for this analysis	
Comparison groups	Intravenous Glutamate infusion v Intravenous Saline infusion (Placebo)

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	t-test, 2-sided

Other pre-specified: Postoperative mortality

End point title	Postoperative mortality
End point description: Safety endpoint	
End point type	Other pre-specified
End point timeframe: Postoperative mortality within 30 days of surgery	

End point values	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	156		
Units: Number of patients	1	6		

Statistical analyses

Statistical analysis title	Postoperative mortality
Statistical analysis description: Postoperative mortality within 30 days	
Comparison groups	Intravenous Glutamate infusion v Intravenous Saline infusion (Placebo)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.12 [4]
Method	Fisher exact

Notes:

[3] - Safety endpoint

[4] - Fisher exact test, two-tailed

Other pre-specified: Postoperative stroke < 24 hours

End point title	Postoperative stroke < 24 hours
End point description: Safety endpoint	
End point type	Other pre-specified
End point timeframe: Postoperative stroke < 24 hours of surgery	

End point values	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150[5]	156[6]		
Units: Number of patients	0	4		

Notes:

[5] - 5 patients did not receive the infusion because of intraoperative exclusion criteria

[6] - 3 patients did not receive the infusion because of intraoperative exclusion criteria

Statistical analyses

Statistical analysis title	Posotperative stroke < 24 hours of surgery
Statistical analysis description: Fisher exact test, two-tailed	
Comparison groups	Intravenous Glutamate infusion v Intravenous Saline infusion (Placebo)
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.12
Method	Fisher exact

Notes:

[7] - Safety analysis

Other pre-specified: SUSAR

End point title	SUSAR
End point description: Safety endpoint	
End point type	Other pre-specified
End point timeframe: SUSAR during the first postoperative day	

End point values	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150[8]	156[9]		
Units: Number of patients	0	0		

Notes:

[8] - 5 patients did not receive the infusion because of intraoperative exclusion criteria

[9] - 3 patients did not receive the infusion because of intraoperative exclusion criteria

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded within 30 days after cardiac surgery

Adverse event reporting additional description:

Safety endpoints postop mortality, stroke < 24 h of surgery, and SUSAR are presented in the endpoints section.

Adverse events directly related to glutamate infusion were not detected. Adverse events typical to cardiac surgery did not differ significantly between study groups. DOI 10.1371/journal.pmed.1003997

Assessment type	Systematic

Dictionary used

Dictionary name	according to GCP
Dictionary version	1

Reporting groups

Reporting group title	Intravenous Glutamate infusion

Reporting group description:

SAE includes postoperative mortality, stroke, postoperative heart failure, acute kidney injury, reoperation for bleeding or infection, and all other AE resulting in hospital stay longer than 7 days. Atrial fibrillation for instance can be both SAE and AE.

Reporting group title	Intravenous Saline infusion (Placebo)

Reporting group description:

SAE includes postoperative mortality, stroke, postoperative heart failure, acute kidney injury, reoperation for bleeding or infection, and all other AE resulting in hospital stay longer than 7 days. Atrial fibrillation for instance can be both SAE and AE.

Serious adverse events	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 150 (46.00%)	92 / 156 (58.97%)	
number of deaths (all causes)	1	6	
number of deaths resulting from adverse events	1	6	
Surgical and medical procedures			
Postoperative complications	Additional description: SAE includes postoperative mortality, stroke, postoperative heart failure, stroke, acute kidney injury, reoperation for bleeding and infection and all other AE associated with hospital stay exceeding 7 days		
subjects affected / exposed	69 / 150 (46.00%)	92 / 156 (58.97%)	
occurrences causally related to treatment / all	0 / 99	0 / 134	
deaths causally related to treatment / all	0 / 1	0 / 6	

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

Non-serious adverse events	Intravenous Glutamate infusion	Intravenous Saline infusion (Placebo)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 150 (20.67%)	30 / 156 (19.23%)	
Surgical and medical procedures			
Atrial Fibrillation	Additional description: Reflects Atrial Firbrillation not associated with extended hospital stay.		
subjects affected / exposed	31 / 150 (20.67%)	30 / 156 (19.23%)	
occurrences (all)	31	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	The planned sample size was reduced from 1400 patients to 310 patients. The initial protocol was based on clinical endpoints for postoperative heart failure, which required a larger sample size. Due to insufficient funding, the clinical endpoints were replaced by NT-proBNP, a biomarker of myocardial dysfunction*. Sample size estimation suggested a total of 310 patients to be sufficient. *The rise in postoperative NT-proBNP is reported to be associated with postoperative heart failure, morbidity, and mortality. In addition, a good agreement was found between the hemodynamic and clinical criteria used for postoperative heart failure in the first GLUTAMICS trial and postoperative NT-proBNP levels. Two sites and three new investigators were added.
20 November 2015	Cardiac and procedure-related risk factors required for EuroSCORE II >= 3.0 were specified. Left ventricular ejection fraction <= 0.30 added to inclusion criteria. A new center and a new investigator were added.
05 September 2016	Exclusion criteria were modified. Inotropic treatment before surgery is not an exclusion criterion if given preemptively. A new site and two new investigators were added.
21 September 2017	The shelf life of study solutions was extended and the infusion bottles were relabeled following pharmaceutical quality control as required by the Swedish MPA.

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.

The proportion of patients with diabetes had almost doubled to 47% compared with the first GLUTAMICS trial. Gutamate does not benefit diabetic hearts, due to downregulation of mitochondrial glutamate transporter EAAT1.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35533197

http://www.ncbi.nlm.nih.gov/pubmed/37657522

http://www.ncbi.nlm.nih.gov/pubmed/38252440

http://www.ncbi.nlm.nih.gov/pubmed/37365871