Clinical trial results:
Effects of Metformin on portal hypertension in patients with cirrhosis.

Summary

EudraCT number	2017-001132-19
Trial protocol	DK
Global end of trial date	12 March 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2021
First version publication date	09 September 2021
Summary attachment (see zip file)	DOI to manuscripts (DOI_metformin.docx)

Trial information

Trial identification

Sponsor protocol code	1-10-72-67-17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University
Sponsor organisation address	Hedeager 3, 2nd floor, Aarhus N, Denmark, 8200
Public contact	Steno Diabetes Center Aarhus, Aarhus University Hospital , 0045 61714731, nikolaj.rittig@clin.au.dk
Scientific contact	Steno Diabetes Center Aarhus, Aarhus University Hospital , 0045 61714731, nikolaj.rittig@clin.au.dk

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	12 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2021
Global end of trial reached?	Yes
Global end of trial date	12 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the study is to investigate if Metformin lowers portal blood pressure in patients with cirrhosis.

Protection of trial subjects:

No specific measures were put in place. Trial subjects were investigated during planned clinical procedures and received standard clinical care and treatment.

Background therapy:

All trial subjects had catheters placed in the hepatic vein (n=32) or portal vein (n=9) + in the femoral artery (n=32) or hand vein (n=9). Catheters were used to measure pressure + obtain blood.

Evidence for comparator:

Animal studies indicate that portal pressure declines and lactate levels increases following metformin consumption - thus a clinical relevant dose of metformin was tested against placebo treatment to investigate whether these effects translates into humans.

Actual start date of recruitment	01 January 2018
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	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	29
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was carried out during the period January 2018 until September 2020, at the Department of Hepatology & Gastroenterology, Aarhus University Hospital, 8200 Aarhus N, DK.
Trial subjects were recruited trough the outpatient clinic when referred to liver vein catheterization (LVC) or transjugular intrahepatic portosystemic shunt (TIPS).

Pre-assignment

Screening details:

Inclusion: 18 years, cirrhosis, informed consent, clinical indication for liver vein catherization (LVC) or transjugular intrahepatic portosystemic shunt (TIPS)
Exclusion: Child pugh class >12, pregnancy/nursing, incapable to understand/read Danish, known allergies/side effects to metformin, eGFR<30 ml

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

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

Blinding implementation details:

Two GCP-experienced personal without any other relation to the study placed either a 1000 mg pill of metformin Activas (Teva pharmaceuticals Industries, US) or placebo (Glostrup Pharmacy, Denmark) in sealed opaque envelopes marked with a unique identification number. Block randomized, metformin and placebo (2:2). A nurse without any other relation to the study blindly drew an envelope and crushed the pill inside before diluting it in approximately 50 ml of tap water and serving it.

Arms

Are arms mutually exclusive?	Yes
Arm title	LVC - metformin

Arm description:

1000 mg metformin

Arm type	Active comparator
Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

1000 mg metformin crushed and dissolved in 50 ml tap water.

Arm title	LVC- placebo

Arm description:

Placebo

Arm type	Placebo

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

A placebo tablet dissolved in 50 ml tap water.

Arm title	TIPS - portal vein

Arm description:

All trial subjects (TIPS) received a single dose metformin

Arm type	Experimental
Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

1000 mg metformin was dissolved in 50 ml tap water and served for the trial subjects.

Arm title	TIPS - arterialized blood

Arm description:

Systemic blood

Arm type	Other sampling site

No investigational medicinal product assigned in this arm

Number of subjects in period 1	LVC - metformin	LVC- placebo	TIPS - portal vein
Started	16	16	4
Completed	16	16	4

Number of subjects in period 1	TIPS - arterialized blood
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Entire study
Reporting group description: -	

Reporting group values	Entire study	Total	
Number of subjects	40	40	
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)	29	29	
From 65-84 years	11	11	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	17	17	
Male	23	23	

Subject analysis sets	
Subject analysis set title	LVC
Subject analysis set type	Per protocol
Subject analysis set description: The patients tested during LVC.	
Subject analysis set title	TIPS
Subject analysis set type	Per protocol
Subject analysis set description: The trial subjects with TIPS.	

Reporting group values	LVC	TIPS	
Number of subjects	32	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)	24	5	

From 65-84 years	8	4	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female	15	1	
Male	17	3	

End points

End points reporting groups

Reporting group title	LVC - metformin
Reporting group description: 1000 mg metformin	
Reporting group title	LVC- placebo
Reporting group description: Placebo	
Reporting group title	TIPS - portal vein
Reporting group description: All trial subjects (TIPS) received a single dose metformin	
Reporting group title	TIPS - arterialized blood
Reporting group description: Systemic blood	
Subject analysis set title	LVC
Subject analysis set type	Per protocol
Subject analysis set description: The patients tested during LVC.	
Subject analysis set title	TIPS
Subject analysis set type	Per protocol
Subject analysis set description: The trial subjects with TIPS.	

Primary: HVPG

End point title	HVPG
End point description:	
End point type	Primary
End point timeframe: difference between baseline and 90 min value	

End point values	LVC - metformin	LVC- placebo	TIPS - portal vein	TIPS - arterialized blood
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	4[1]	4[2]
Units: mmHg				
arithmetic mean (confidence interval 95%)	-2.9 (-5.1 to -0.7)	0.9 (-1 to 2.7)	1 (1 to 1)	1 (1 to 1)

Notes:

[1] - N/A

[2] - N/A

Attachments (see zip file)	fig 1/Figures_LVK1600600.tiff fig 2/Figures_LVK2600600.tiff Figures_LVK3600600.tiff_new.jpg

	fig 4/Figures_LVK4600600.tiff tables_LVK.docx

Statistical analyses

Statistical analysis title	Two-way RM ANOVA
Comparison groups	LVC - metformin v LVC- placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA

Primary: Lactate

End point title	Lactate

End point description:

End point type	Primary

End point timeframe:

baseline - 90 min

End point values	LVC - metformin	LVC- placebo	TIPS - portal vein	TIPS - arterialized blood
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[3]	16[4]	4[5]	4
Units: procent				
arithmetic mean (confidence interval 95%)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	1.23 (1.06 to 1.4)

Notes:

[3] - N/A

[4] - N/A

[5] - 8 individuals - there own "control". Portal vs arterialized blood

End point values	TIPS			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: procent				
arithmetic mean (confidence interval 95%)	23 (6 to 40)			

Attachments (see zip file)	fig1/Figure 1.tiff fig2/Figure 2.tiff

fig3/Figure 3.tiff

Statistical analyses

Statistical analysis title	2-way RM ANOVA and posthoc t-test
Comparison groups	TIPS - portal vein v TIPS - arterialized blood
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	post hoc t-test
Parameter estimate	Mean difference (final values)
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	40
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 hours	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	Total

Reporting group description: -

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 40 (12.50%)		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2019	Invitation to the TIPS project by letter (chronic TIPS inclusion) and prolonged the period to include patients.

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/34165199

http://www.ncbi.nlm.nih.gov/pubmed/34331316