Clinical trial results:
Brain muscle axis during treatment of hepatic encephalopathy with L-ornithine L-aspartate

Summary

EudraCT number	2012-003817-32
Trial protocol	GB
Global end of trial date	19 June 2015

Results information

Result version number	v1 (current)
This version publication date	30 July 2020
First version publication date	30 July 2020
Summary attachment (see zip file)	LOLA results presented in ISHEN 2016 and published in J HEP (ISHEN2017YP.pdf)

Trial information

Trial identification

Sponsor protocol code	LOLA-Merz:WMDHP39937

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01847651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Wharf Road, London, United Kingdom,
Public contact	Dr Yasmin Pasha, Imperial College London, +44 02078866454, y.pasha@imperial.ac.uk
Scientific contact	Professor Simon Taylor-Robinson, Imperial College London, +44 02078866454, s.taylor-robinson@imperial.ac.uk

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 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2015
Global end of trial reached?	Yes
Global end of trial date	19 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: Improvement in mental state by paper-and-pencil-based Psychometric Hepatic Encephalopathy Score (PHES) and Cogstate Research test(computer-based cognitive assessment research tool)

Protection of trial subjects:

Initial REC recommendation was to exclude subjects with renal impairment from screening, the Patient consent form reflects this. A metal safety questionnaire was carried out at screening visit and each study visit and signed afresh prior to each MRI scan.

Prior to each study visit the subjects underwent consent for ongoing trial participation muscle biopsies and scans. I regularly screened for side effects and effects. I also gave my contact details and email which was checked daily for either any complications of study procedures ie muscle biopsy. The contact details for the nursing staff at the liver day unit were also provided, these staff knew the study protocol and had access to my mobile number even out of hours, in case of an emergency. I asked nurses on liver day unit to collect written feedback questionnaires post muscle biopsy.

Background therapy:

Those already on lactulose could remain on it however during the study period. However subjects could not go on lactulose during 12 week study period, if not on it at study start but they were free to do so afterwards. If a subject received a liver transplant or antibiotics (unless taken for unrelated condition) or experienced a GI Bleed during this 12 weeks their data would also be excluded.

Evidence for comparator: -

Actual start date of recruitment	27 August 2013
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	United Kingdom: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study powered at n=34. Recruitment occurred from screened patients who gave their consent at St Mary's Hospital Cirrhosis Clinic. The screening began in May 2013. The first patient first visit occurred on 23/08/2013 and the last patient's last visit occurred on 19/06/2015.

Pre-assignment

Screening details:

I performed all screening visits and recruitment in accordance with inclusion and exclusion criteria. 102 patients were screened. 69 met criteria (33 did not) and consented for screening.

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, Data analyst, Carer, Assessor

Blinding implementation details:

Envelopes containing unblinding information for each pharmacy pack number for unblinding were kept in Imperial Research Pharmacy. These were not accessed until after data collection and subject participation was complete

Arms

Are arms mutually exclusive?	Yes
Arm title	L-ORNITHINE L-ASPARTATE (LOLA)

Arm description:

LOLA taken at 6g tds for 12 weeks total

Arm type	Active comparator
Investigational medicinal product name	L-ornithine-L aspartate
Investigational medicinal product code	LOLA
Other name	
Pharmaceutical forms	Effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

6g orally three times a day, 2 sachets to be dissolved fully in 1 cup cold water or cordial taken three times a day

Arm title	Placebo

Arm description:

Identical orange flavour granules to IMP were prepared and supllied in identical packaging by Merz Phramceuticals

Arm type	Placebo
Investigational medicinal product name	Dummy LOLA/Placebo
Investigational medicinal product code	LOLA
Other name	Placebo
Pharmaceutical forms	Effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

6g orally three times a day, 2 sachet to be dissolved fully in 1 cup cold water or cordial taken three times a day

Number of subjects in period 1	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo
Started	14	20
Completed	14	20

Baseline characteristics

Reporting groups	
Reporting group title	L-ORNITHINE L-ASPARTATE (LOLA)
Reporting group description:	
LOLA taken at 6g tds for 12 weeks total	
Reporting group title	Placebo
Reporting group description:	
Identical orange flavour granules to IMP were prepared and suplliedin identical packaging by Merz Phramceuticals	

Reporting group values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo	Total
Number of subjects	14	20	34
Age categorical			
36 subject aged 30-64 at recruitment 2 subjects aged 65 at recruitment			
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)	14	20	34
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
unkown	14	20	34

Subject analysis sets	
Subject analysis set title	baseline differences between groups
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
34 Subjects completed the trial. After unblinding 14 were in Treatment Arm and 20 in the Placebo group. There were no significant baseline differences between groups at the outset	

Reporting group values	baseline differences between groups		
Number of subjects	34		
Age categorical			
36 subject aged 30-64 at recruitment 2 subjects aged 65 at recruitment			
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)	34		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
unkown	34		

End points

End points reporting groups

Reporting group title	L-ORNITHINE L-ASPARTATE (LOLA)
Reporting group description: LOLA taken at 6g tds for 12 weeks total	
Reporting group title	Placebo
Reporting group description: Identical orange flavour granules to IMP were prepared and supplliedin identical packaging by Merz Phramceuticals	
Subject analysis set title	baseline differences between groups
Subject analysis set type	Sub-group analysis
Subject analysis set description: 34 Subjects completed the trial. After unblinding 14 were in Treatment Arm and 20 in the Placebo group. There were no significant baseline differences between groups at the outset	

Primary: Better concentration

End point title	Better concentration[1]
End point description:	
End point type	Primary
End point timeframe: measured at 0, 4 and 12 weeks	

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Better memory

End point title	Better memory[2]
End point description:	
End point type	Primary
End point timeframe: measured at 0, 4 and 12 weeks	

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	4	1		

Statistical analyses

No statistical analyses for this end point

Primary: Better quality sleep

End point title	Better quality sleep[3]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	5	2		

Statistical analyses

No statistical analyses for this end point

Primary: More stamina/strength

End point title	More stamina/strength[4]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Less irritable

End point title	Less irritable[5]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: More energy

End point title	More energy[6]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	8	1		

Statistical analyses

No statistical analyses for this end point

Primary: More rested

End point title	More rested[7]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

Notes:

[7] - 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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: No different

End point title	No different[8]

End point description:

End point type	Primary

End point timeframe:

Measured at 0, 4 and 12 weeks

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: Unknown

End point values	L-ORNITHINE L-ASPARTATE (LOLA)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	20		
Units: Number of subjects reporting effect	6	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

3 subjects in placebo arm were hospitalised following randomisation, 1 for dehydration, one for unrelated orthopaedic fracture, 1 for an unrelated hernia repair surgery. Protocol deemed all hospital admssions to be SAEs

Assessment type	Systematic

Dictionary used

Dictionary name	SAE form completed
Dictionary version	1

Reporting groups

Reporting group title	LOLA

Reporting group description:

Active treatment arm. LOLA taken at 6g tds for 12 weeks total

Reporting group title	Placebo

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: only 3 SAEs recorded in placebo arm of this study

Serious adverse events	LOLA	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	3 / 22 (13.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hernia Repair	Additional description: Long inpatient stay for a subject who underwent hernia repair complicated by ascites and infection this was after he had signed consent to participate so technically he was randomised but did not participate or recieve IMP until over 6 months after		
subjects affected / exposed	0 / 12 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Dehydration	Additional description: patient admitted 2/7 after randomisation due to adjustment of diuretics at another clinic. Rehydrated and discharged		
subjects affected / exposed	0 / 12 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection in skin graft following fracture	Additional description: Infected shin wound following open fracture and skin graft. was inpatient for orthopaedic reasons between week 3-8 of trial so therefore missed visit 2		

subjects affected / exposed	0 / 12 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LOLA	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 22 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported