



## 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:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| 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:

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**General information about the trial**

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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)

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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:

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**Population of trial subjects**

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**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:

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**Subjects enrolled per age group**

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|  |   |
|--|---|
| 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                            |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Identical orange flavour granules to IMP were prepared and supplied in identical packaging by Merz Pharmaceuticals

|  |   |
|--|---|
| 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

| <b>Number of subjects in period 1</b> | <b>L-ORNITHINE L-ASPARTATE (LOLA)</b> | <b>Placebo</b> |
|---------------------------------------|---------------------------------------|----------------|
| 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 supplied in identical packaging by Merz Pharmaceuticals |                                |

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

### Primary: Better concentration

|   |                                     |
|---|-------------------------------------|
| End point title   | Better concentration <sup>[1]</sup> |
| End point description:  |                                     |
| End point type  | Primary                             |
| End point timeframe:<br>measured at 0, 4 and 12 weeks   |                                     |
| Notes:<br>[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.<br>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 <sup>[2]</sup> |
| End point description:                                |                              |
| End point type  | Primary                      |
| End point timeframe:<br>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<br>L-ASPARTATE<br>(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 <sup>[3]</sup> |
|-----------------|-------------------------------------|

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<br>L-ASPARTATE<br>(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 <sup>[4]</sup> |
|-----------------|--------------------------------------|

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<br>L-ASPARTATE<br>(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 <sup>[5]</sup> |
|-----------------|-------------------------------|

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<br>L-ASPARTATE<br>(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 <sup>[6]</sup> |
|-----------------|----------------------------|

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<br>L-ASPARTATE<br>(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 <sup>[7]</sup> |
|-----------------|----------------------------|

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<br>L-ASPARTATE<br>(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 <sup>[8]</sup> |
|-----------------|-----------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Measured at 0, 4 and 12 weeks

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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

|  |                                      |                 |  |  |
|--|--------------------------------------|-----------------|--|--|
| <b>End point values</b>                    | L-ORNITHINE<br>L-ASPARTATE<br>(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<sup>[1]</sup>

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 admissions 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 receive 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 %

| <b>Non-serious adverse events</b>                     | 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported