



Clinical trial results:

The control of brain networks after traumatic brain injury: a neuroimaging and neuropsychological study of dopamine and cognition Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-004244-37 |
| Trial protocol | GB |
| Global end of trial date | 29 September 2016 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 18 December 2019 |
| First version publication date | 15 November 2018 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setNeed to correct the sponsor information. |
| Summary attachment (see zip file) | TBI Dopamine CSR (Clinical Study Report DREAM Trial_19.09.2018.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 13HH1824 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Imperial College London |
| Sponsor organisation address | South Kensington Campus, London, United Kingdom, SW7 2AZ |
| Public contact | Youssouf, Imperial College London, +44 0203 311 0213, nabila.youssouf@imperial.ac.uk |
| Scientific contact | Youssouf, Imperial College London, +44 0203 311 0213, nabila.youssouf@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 | 18 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 September 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1. To investigate the relationship between dopamine levels (a chemical in the brain which modulates brain functions) in the brain and its impact on cognition in patients who have suffered a traumatic brain injury.

Protection of trial subjects:

No specific measures were implemented to protect participants, but adverse events were closely monitored and participants were free to withdraw at any time.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 February 2014 |
| 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: 46 |
| Worldwide total number of subjects | 46 |
| EEA total number of subjects | 46 |

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) | 46 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

158 TBI participants were screened. 62 chose not to participate and 50 met one or more of the exclusion criteria.

Period 1

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

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo First |

Arm description:

participants in this arm received placebo first.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

As per IMP

| | |
|------------------|-----------------------|
| Arm title | Methylphenidate First |
|------------------|-----------------------|

Arm description:

participants in this arm received the active IMP first before crossing over to placebo

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Methylphenidate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

0.3mg/kg (rounded to nearest 5mg and capped at maximum dose of 25mg/day) twice per day.

| Number of subjects in period 1^[1] | Placebo First | Methylphenidate First |
|---|---------------|-----------------------|
| Started | 20 | 20 |
| Completed | 20 | 20 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: See CSR

Baseline characteristics

Reporting groups

| | |
|--|-----------------------|
| Reporting group title | Placebo First |
| Reporting group description: participants in this arm received placebo first. | |
| Reporting group title | Methylphenidate First |
| Reporting group description: participants in this arm received the active IMP first before crossing over to placebo | |

| Reporting group values | Placebo First | Methylphenidate First | Total |
|--|---------------|-----------------------|-------|
| Number of subjects | 20 | 20 | 40 |
| 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 | 20 | 40 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 2 | 6 |
| Male | 16 | 18 | 34 |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | Normal Caudate |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Normal caudate 123I-ioflupane specific binding ratio (N=22) Comparison of IMP group median score vs placebo group median score | |
| Subject analysis set title | Low Caudate Group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Low caudate 123I-ioflupane specific binding ratio (N=18) Comparison of IMP group median score vs placebo group median score | |

| Reporting group values | Normal Caudate | Low Caudate Group | |
|--|----------------|-------------------|--|
| Number of subjects | 22 | 18 | |
| 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) | 22 | 18 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 1 | |
| Male | 17 | 17 | |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | Placebo First |
| Reporting group description: participants in this arm received placebo first. | |
| Reporting group title | Methylphenidate First |
| Reporting group description: participants in this arm received the active IMP first before crossing over to placebo | |
| Subject analysis set title | Normal Caudate |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Normal caudate 123I-ioflupane specific binding ratio (N=22) Comparison of IMP group median score vs placebo group median score | |
| Subject analysis set title | Low Caudate Group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Low caudate 123I-ioflupane specific binding ratio (N=18) Comparison of IMP group median score vs placebo group median score | |

Primary: Primary Outcome Measure

| | |
|---|--|
| End point title | Primary Outcome Measure ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: Assessed by comparing scores at placebo visit to those at active IMP visit. | |
| 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: See CSR | |

| End point values | Normal Caudate | Low Caudate Group | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22 | 18 | | |
| Units: Milliseconds | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Placebo | 357 (325 to 392) | 382 (359 to 429) | | |
| Methylphenidate | 362 (331 to 378) | 369 (347 to 398) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

From consent to the final MRI study visit.

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

Dictionary used

| | |
|-----------------|------|
| Dictionary name | None |
|-----------------|------|

| | |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | All participants |
|-----------------------|------------------|

Reporting group description:

All participants affected by adverse events (n=24/40).

| Serious adverse events | All participants | | |
|---|------------------|--|--|
| 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 | All participants | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |

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: There were no serious adverse events. One participant discontinued methylphenidate and withdrew from the trial due to unpleasant feelings of restlessness that were considered likely secondary to the treatment. Heart rate was significantly increased on methylphenidate compared to placebo (median change = 5.5 beats per minute; 95% CI [3, 12]; $P < 0.001$). Systolic blood pressure was not different between methylphenidate and placebo (median change = 1.5 mmHg; 95% CI [-2.5, 8]; $P = 0.21$).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|----------------------|
| 21 February 2014 | Protocol amendment 1 |
| 05 March 2014 | Protocol amendment 2 |
| 13 June 2014 | Protocol amendment 3 |
| 21 October 2014 | Protocol amendment 4 |
| 12 November 2014 | Protocol amendment 5 |
| 19 July 2016 | Protocol amendment 6 |

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.

See the attached CSR for a complete description of the study, results and conclusions.

Notes: