



## Clinical trial results:

### Phase II triple blind placebo controlled RCT of simvastatin treatment for autism in young children with Neurofibromatosis Type 1

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-005742-38   |
| Trial protocol           | GB               |
| Global end of trial date | 30 November 2015 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 May 2020  |
| First version publication date | 13 May 2020  |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | R02145 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                           |
|------------------------------------|---------------------------|
| ISRCTN number                      | -                         |
| ClinicalTrials.gov id (NCT number) | -                         |
| WHO universal trial number (UTN)   | -                         |
| Other trial identifiers            | REC reference: 13/NW/0111 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Manchester University NHS Foundation Trust  |
| Sponsor organisation address | Oxford Road, Manchester, United Kingdom,  |
| Public contact               | Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk |
| Scientific contact           | Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.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                       | 30 November 2015 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 30 November 2015 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 November 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:

The overall research aim is to determine whether treatment with statins improves the ASD phenotype in children with NF1 autism. This aim of this study is to test:

- Acceptability and feasibility of involvement for families of children with NF1 ASD
- The feasibility and acceptability of the assessment protocol
- Treatment effects on intermediate and endpoint behavioural phenotype measures and imaging parameters

The hypothesis is that treatment with statins in young children with NF1 autism will be:

- Feasible, safe and acceptable to families
- Associated with signals of change in brain imaging parameters
- Associated with signals of change in autism and other behavioural symptoms

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Protection of trial subjects:

Risks and burdens identified to the participants include the burden of travel to research site, possible distress caused by blood tests and brain scan and the risk associated with the treatment. The protocol has been designed to reduce these risks as following:

Burden of travel: The study has been designed with careful consideration of the burden on the participants. The trial team has sought to keep the burden of the treatment visits and intervention to the absolute minimum possible whilst at the same time ensuring safety of participants. The initial screening will be via postal questionnaire and the followup at 16 weeks via a telephone call in order to reduce the number of participant visits.

Possible distress due to blood tests and brain scan: Experienced paediatric nurses will carry out blood tests. Play therapist will be used to help explain the procedures to the children in a developmentally appropriate way.

Risks associated with medication: Stringent monitoring of adverse effects of medication will be carried out during the course of treatment. This will include both verbal enquiry as well as blood tests. The statin expert on the team (AM) has extensive clinical experience of the use of statins in very young children. He will be available for advice and for monitoring the results of the blood tests.

Confidentiality; The research team will have access to person identifiable information only when they receive the screening pack back from parents. No person identifiable information will be used in any publication/advertisement of the trial. Parents will be explained that all the assessments will be confidential and that confidentiality will be maintained at all times other than when the participant is identified as being at serious risk (such as child protection issues). In such cases, the information will be discussed with the CI and anonymously discussed with the child protection lead nurse at MFT.

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Background therapy:

N/A

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Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 30 September 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

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|                                      |                    |
|--------------------------------------|--------------------|
| 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 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 34 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment start date: 30/09/2013

Recruitment end date: 30/11/2015

Territory: UK only

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                            |    |
|----------------------------|----|
| Number of subjects started | 34 |
|----------------------------|----|

|                              |    |
|------------------------------|----|
| Number of subjects completed | 30 |
|------------------------------|----|

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
|----------------------------|---------------------------------|

|                            |                      |
|----------------------------|----------------------|
| Reason: Number of subjects | Not NF1 diagnosis: 2 |
|----------------------------|----------------------|

### 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, Carer |
|---------------|------------------------------|

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

Arm description: -

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |         |
|--|---------|
| Investigational medicinal product name | Placebo |
|--|---------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |                 |
|----------------------|-----------------|
| Pharmaceutical forms | Oral suspension |
|----------------------|-----------------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

N/A - placebo

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

Arm description:

Intervention arm

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |             |
|--|-------------|
| Investigational medicinal product name | Simvastatin |
|--|-------------|

|  |               |
|--|---------------|
| Investigational medicinal product code | PL 00427/0146 |
|--|---------------|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |                 |
|----------------------|-----------------|
| Pharmaceutical forms | Oral suspension |
|----------------------|-----------------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

0.5mg/kg/dau in a single dose or placebo for 4 weeks. Those showing no significant adverse events after 4 weeks, will be escalated to a dose of 1mg/kg/day to a maximum of 30 mg/day in a single daily dose for a further 8 weeks

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo | Simvastatin |
|---|---------|-------------|
| Started   | 16      | 14          |
| Completed   | 15      | 11          |
| Not completed                                       | 1       | 3           |
| Lost to follow-up                                   | 1       | 2           |
| Consent withdrawn                                   | -       | 1           |

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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: Four participants were withdrawn from the trial prior to randomisation: two withdrew and two proved not to have NF1 diagnosis.

## Baseline characteristics

### Reporting groups

|                                |             |
|--------------------------------|-------------|
| Reporting group title          | Placebo     |
| Reporting group description: - |             |
| Reporting group title          | Simvastatin |
| Reporting group description:   |             |
| Intervention arm               |             |

| Reporting group values                             | Placebo | Simvastatin | Total |
|--|---------|-------------|-------|
| Number of subjects                                 | 16      | 14          | 30    |
| 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)                              | 16      | 14          | 30    |
| Adolescents (12-17 years)                          | 0       | 0           | 0     |
| Adults (18-64 years)                               | 0       | 0           | 0     |
| From 65-84 years                                   | 0       | 0           | 0     |
| 85 years and over                                  | 0       | 0           | 0     |
| Age continuous                                     |         |             |       |
| Units: years                                       |         |             |       |
| arithmetic mean                                    | 8.28    | 7.90        |       |
| standard deviation                                 | ± 1.76  | ± 1.90      | -     |
| Gender categorical                                 |         |             |       |
| Units: Subjects                                    |         |             |       |
| Female   | 2       | 4           | 6     |
| Male   | 14      | 10          | 24    |
| Mutation   |         |             |       |
| Units: Subjects                                    |         |             |       |
| Inherited  | 10      | 3           | 13    |
| De novo  | 5       | 11          | 16    |
| Not recorded                                       | 1       | 0           | 1     |
| Riccardi Scale                                     |         |             |       |
| Units: Subjects                                    |         |             |       |
| one  | 3       | 4           | 7     |
| two  | 12      | 5           | 17    |
| three  | 0       | 4           | 4     |
| four   | 1       | 1           | 2     |
| Parent-Nominated Target Symptoms: Hyperactivity    |         |             |       |
| Units: Subjects                                    |         |             |       |
| Yes  | 6       | 7           | 13    |
| No   | 10      | 7           | 17    |
| Parent-nominated target symptoms: Aggression       |         |             |       |

|   |        |        |    |
|---|--------|--------|----|
| Units: Subjects   |        |        |    |
| Yes   | 6      | 7      | 13 |
| No  | 10     | 7      | 17 |
| Parent-nominated target symptoms:<br>Social inappropriateness     |        |        |    |
| Units: Subjects   |        |        |    |
| Yes   | 9      | 9      | 18 |
| No  | 7      | 5      | 12 |
| Parent-nominated target symptoms:<br>Problems with communication  |        |        |    |
| Units: Subjects   |        |        |    |
| Yes   | 3      | 2      | 5  |
| No  | 13     | 12     | 25 |
| Parent-nominated target symptoms:<br>Inflexibility/obsessionality |        |        |    |
| Units: Subjects   |        |        |    |
| Yes   | 7      | 2      | 9  |
| No  | 9      | 12     | 21 |
| Parent-nominated target characteristics:<br>Learning problems     |        |        |    |
| Units: Subjects   |        |        |    |
| Yes   | 1      | 2      | 3  |
| No  | 15     | 12     | 27 |
| Weight  |        |        |    |
| Units: kg   |        |        |    |
| arithmetic mean   | 29.85  | 25.76  |    |
| standard deviation  | ± 8.51 | ± 6.08 | -  |
| Social Responsiveness Scale: T Score                              |        |        |    |
| Units: Scale  |        |        |    |
| arithmetic mean   | 83.06  | 82.93  |    |
| standard deviation  | ± 7.58 | ± 8.67 | -  |
| Social interaction  |        |        |    |
| Autism Diagnostic interview scale: Total A                        |        |        |    |
| Units: Scale  |        |        |    |
| arithmetic mean   | 18.88  | 16.29  |    |
| standard deviation  | ± 5.08 | ± 5.08 | -  |
| Social communication  |        |        |    |
| Autism diagnostic interview: Total B                              |        |        |    |
| Units: Scale  |        |        |    |
| arithmetic mean   | 14.19  | 14.00  |    |
| standard deviation  | ± 4.37 | ± 4.02 | -  |
| Restricted repetitive behaviours                                  |        |        |    |
| Autism diagnostic interview: Total C                              |        |        |    |
| Units: Scale  |        |        |    |
| arithmetic mean   | 5.88   | 5.93   |    |
| standard deviation  | ± 2.78 | ± 2.64 | -  |
| ADOS: Social affect   |        |        |    |
| Units: scale  |        |        |    |
| arithmetic mean   | 10.13  | 9.29   |    |
| standard deviation  | ± 3.26 | ± 3.24 | -  |
| ADOS: RRB   |        |        |    |
| Units: Scale  |        |        |    |
| arithmetic mean   | 1.88   | 2.14   |    |

|   |         |         |   |
|---|---------|---------|---|
| standard deviation                                    | ± 1.63  | ± 1.74  | - |
| ADOS: Total   |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 12.00   | 11.57   |   |
| standard deviation                                    | ± 3.81  | ± 3.96  | - |
| WASI verbal IQ  |         |         |   |
| n= 26   |         |         |   |
| Units: score  |         |         |   |
| arithmetic mean                                       | 81.57   | 90.00   |   |
| standard deviation                                    | ± 12.99 | ± 11.24 | - |
| Aberrant Behaviour Checklist: Irritability            |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 19.40   | 24.21   |   |
| standard deviation                                    | ± 10.38 | ± 9.36  | - |
| Aberrant Behaviour Checklist: Lethargy                |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 14.20   | 16.08   |   |
| standard deviation                                    | ± 8.36  | ± 6.85  | - |
| Aberrant behaviour checklist:<br>Stereotypy           |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 4.87    | 7.29    |   |
| standard deviation                                    | ± 3.56  | ± 5.04  | - |
| Aberrant Behaviour Checklist:<br>Hyperactivity        |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 24.07   | 30.21   |   |
| standard deviation                                    | ± 13.04 | ± 8.75  | - |
| Aberrant Behaviour Checklist:<br>Inappropriate speech |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 5.93    | 7.43    |   |
| standard deviation                                    | ± 3.15  | ± 3.61  | - |
| Clinical Global Impression: Severity of<br>illness    |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 3.88    | 3.57    |   |
| standard deviation                                    | ± 0.885 | ± 0.646 | - |
| Conners 3 Parent Rating Scale:<br>Inattention         |         |         |   |
| Units: Score  |         |         |   |
| arithmetic mean                                       | 79.73   | 80.71   |   |
| standard deviation                                    | ± 12.13 | ± 9.36  | - |
| Conners 3 Parent Rating Scale:<br>Hyperactivity       |         |         |   |
| Units: score  |         |         |   |
| arithmetic mean                                       | 71.87   | 81.14   |   |
| standard deviation                                    | ± 14.75 | ± 8.88  | - |



## End points

### End points reporting groups

|                                |             |
|--------------------------------|-------------|
| Reporting group title          | Placebo     |
| Reporting group description: - |             |
| Reporting group title          | Simvastatin |
| Reporting group description:   |             |
| Intervention arm               |             |

### Primary: Parent defined target symptoms (PDTs)

|                        |  |
|------------------------|--|
| End point title        | Parent defined target symptoms (PDTs) <sup>[1]</sup> |
| End point description: |  |

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

End point timeframe:

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: These are descriptive endpoints only

| End point values                     | Placebo         | Simvastatin     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 12              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 3.516 (± 1.768) | 3.250 (± 1.684) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Completed imaging assessments

|                        |  |
|------------------------|--|
| End point title        | Completed imaging assessments <sup>[2]</sup> |
| End point description: |  |

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

End point timeframe:

Study duration

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: These are descriptive endpoints only

| End point values            | Placebo         | Simvastatin     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 16              | 14              |  |  |
| Units: Subjects             |                 |                 |  |  |
| Yes                         | 15              | 11              |  |  |
| No                          | 1               | 3               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: ABC: Irritability

|  |                   |
|--|-------------------|
| End point title                        | ABC: Irritability |
| End point description:                 |                   |
| Individual components of the ABC scale |                   |
| End point type                         | Secondary         |
| End point timeframe:                   |                   |
| 12 weeks                               |                   |

| End point values                     | Placebo         | Simvastatin     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 13              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 16.40 (± 10.82) | 22.31 (± 12.14) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title              | ABC: Irritability              |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.66                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.61                          |
| upper limit                             | 7.93                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.2                            |

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**Secondary: ABC: Lethargy**

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|                 |               |
|-----------------|---------------|
| End point title | ABC: Lethargy |
|-----------------|---------------|

End point description:

Component of the ABC scale

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

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| End point values                     | Placebo         | Simvastatin     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 12              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 10.53 (± 9.61)  | 15.25 (± 10.30) |  |  |

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**Statistical analyses**

|                                   |               |
|-----------------------------------|---------------|
| <b>Statistical analysis title</b> | ABC: Lethargy |
|-----------------------------------|---------------|

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Placebo v Simvastatin |
|-------------------|-----------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 27 |
|---|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |       |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

|                    |                                |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

|                |     |
|----------------|-----|
| Point estimate | 3.6 |
|----------------|-----|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |       |
|-------------|-------|
| lower limit | -4.09 |
|-------------|-------|

|             |       |
|-------------|-------|
| upper limit | 11.28 |
|-------------|-------|

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
|----------------------|----------------------------|

|                  |      |
|------------------|------|
| Dispersion value | 3.92 |
|------------------|------|

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**Secondary: ABC: Stereotypy**

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|                 |                 |
|-----------------|-----------------|
| End point title | ABC: Stereotypy |
|-----------------|-----------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

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| End point values                     | Placebo            | Simvastatin        |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 15                 | 13                 |  |  |
| Units: Scale                         |                    |                    |  |  |
| arithmetic mean (standard deviation) | 3.93 ( $\pm$ 3.63) | 7.77 ( $\pm$ 5.83) |  |  |

### Statistical analyses

| Statistical analysis title              | ABC: Stereotypy                |
|---|--------------------------------|
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.32                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.98                          |
| upper limit                             | 4.2                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.32                           |

### Secondary: ABC: Hyperactivity

|                        |                    |
|------------------------|--------------------|
| End point title        | ABC: Hyperactivity |
| End point description: |                    |
| End point type         | Secondary          |
| End point timeframe:   |                    |
| 12 weeks               |                    |

| End point values                     | Placebo              | Simvastatin          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 15                   | 11                   |  |  |
| Units: Scale                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 19.13 ( $\pm$ 13.17) | 28.77 ( $\pm$ 12.83) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | ABC: Hyperactivity             |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 26                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 3.87                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -3.28                          |
| upper limit                             | 11.01                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.65                           |

### Secondary: ABC: Inappropriate speech

|                        |                           |
|------------------------|---------------------------|
| End point title        | ABC: Inappropriate speech |
| End point description: |                           |
| End point type         | Secondary                 |
| End point timeframe:   |                           |
| 12 weeks               |                           |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | Placebo         | Simvastatin     |  |  |
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 11              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 4.80 (± 2.54)   | 7.15 (± 3.31)   |  |  |

### Statistical analyses

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | ABC: Inappropriate speech |
| Comparison groups                 | Placebo v Simvastatin     |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 26                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.77                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.1                           |
| upper limit                             | 3.63                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.95                           |

### Secondary: 25% reduction irritability scale

|                        |                                  |
|------------------------|----------------------------------|
| End point title        | 25% reduction irritability scale |
| End point description: |                                  |
|                        |                                  |
| End point type         | Secondary                        |
| End point timeframe:   |                                  |
| 12 weeks               |                                  |

| End point values            | Placebo         | Simvastatin     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 15              | 13              |  |  |
| Units: Subjects             |                 |                 |  |  |
| yes                         | 5               | 6               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Conners: Inattention

|                        |                      |
|------------------------|----------------------|
| End point title        | Conners: Inattention |
| End point description: |                      |
|                        |                      |
| End point type         | Secondary            |
| End point timeframe:   |                      |
| 12 weeks               |                      |

| End point values                     | Placebo              | Simvastatin          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 15                   | 13                   |  |  |
| Units: Scale                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 74.53 ( $\pm$ 14.16) | 80.38 ( $\pm$ 10.08) |  |  |

## Statistical analyses

| Statistical analysis title              | Conners: Inattention           |
|---|--------------------------------|
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 5.33                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.96                          |
| upper limit                             | 11.61                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.21                           |

## Secondary: Conners: Hyperactivity

|                        |                        |
|------------------------|------------------------|
| End point title        | Conners: Hyperactivity |
| End point description: |                        |
| End point type         | Secondary              |
| End point timeframe:   |                        |
| 12 Weeks               |                        |

| End point values                     | Placebo              | Simvastatin          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 15                   | 13                   |  |  |
| Units: Scale                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 69.40 ( $\pm$ 17.12) | 78.31 ( $\pm$ 13.51) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Conners: Hyperactivity         |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.98                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -8.09                          |
| upper limit                             | 6.13                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.63                           |

## Secondary: Conners: Learning problems

|                        |                            |
|------------------------|----------------------------|
| End point title        | Conners: Learning problems |
| End point description: |                            |
| End point type         | Secondary                  |
| End point timeframe:   |                            |
| 12 weeks               |                            |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | Placebo         | Simvastatin     |  |  |
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 13              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 65.40 (± 12.91) | 73.69 (± 15.71) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Conners: Learning problems     |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.59                           |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.13                      |
| upper limit          | 5.3                        |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 1.89                       |

### Secondary: Conners: Executive function

|                        |                             |
|------------------------|-----------------------------|
| End point title        | Conners: Executive function |
| End point description: |                             |
|                        |                             |
| End point type         | Secondary                   |
| End point timeframe:   |                             |
| 12 weeks               |                             |

| End point values                     | Placebo         | Simvastatin     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 15              | 13              |  |  |
| Units: Scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 68.20 (± 16.24) | 76.00 (± 11.66) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Conners: Executive function    |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 4.04                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.51                          |
| upper limit                             | 10.59                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 3.34                           |

### Secondary: Conners: Aggression

|                        |                     |
|------------------------|---------------------|
| End point title        | Conners: Aggression |
| End point description: |                     |
| End point type         | Secondary           |
| End point timeframe:   |                     |
| 12 weeks               |                     |

| End point values                     | Placebo              | Simvastatin          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 15                   | 13                   |  |  |
| Units: Scale                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 68.40 ( $\pm$ 20.86) | 72.77 ( $\pm$ 17.09) |  |  |

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title              | Conners: Aggression            |
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.05                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -11.05                         |
| upper limit                             | 10.96                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 5.61                           |

### Secondary: Conners: Peer relations

|                        |                         |
|------------------------|-------------------------|
| End point title        | Conners: Peer relations |
| End point description: |                         |
| End point type         | Secondary               |
| End point timeframe:   |                         |
| 12 weeks               |                         |

| End point values                     | Placebo              | Simvastatin         |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 15                   | 13                  |  |  |
| Units: Scale                         |                      |                     |  |  |
| arithmetic mean (standard deviation) | 83.89 ( $\pm$ 11.53) | 86.08 ( $\pm$ 8.73) |  |  |

## Statistical analyses

| Statistical analysis title              | Conners: Peer relations        |
|---|--------------------------------|
| Comparison groups                       | Placebo v Simvastatin          |
| Number of subjects included in analysis | 28                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.38                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.45                          |
| upper limit                             | 7.21                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 2.97                           |

## Secondary: Responders

|                        |            |
|------------------------|------------|
| End point title        | Responders |
| End point description: |            |
| End point type         | Secondary  |
| End point timeframe:   |            |
| 12 weeks               |            |

| End point values            | Placebo         | Simvastatin     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 14              | 12              |  |  |
| Units: Subjects             |                 |                 |  |  |
| PDTS score < 3              | 2               | 5               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Global improvement

End point title Global improvement

End point description:

End point type Secondary

End point timeframe:

12 weeks

| End point values                     | Placebo             | Simvastatin         |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 14                  | 12                  |  |  |
| Units: Scale                         |                     |                     |  |  |
| arithmetic mean (standard deviation) | 3.57 ( $\pm$ 0.852) | 3.00 ( $\pm$ 0.739) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment responder

End point title Treatment responder

End point description:

End point type Secondary

End point timeframe:

12 weeks

| End point values            | Placebo         | Simvastatin     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 14              | 14              |  |  |
| Units: Subjects             |                 |                 |  |  |
| Yes                         | 0               | 3               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events will be recorded and reported at each study visit. Serious Adverse Event (SAE) forms. SAEs and SUSARs will be reported to the sponsor in accordance with the relevant local SOPs.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |   |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

|                       |             |
|-----------------------|-------------|
| Reporting group title | Simvastatin |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events                            | Placebo        | Simvastatin    |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 16 (0.00%) | 0 / 14 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |

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

| Non-serious adverse events                            | Placebo           | Simvastatin       |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 16 / 16 (100.00%) | 14 / 14 (100.00%) |  |
| General disorders and administration site conditions  |                   |                   |  |
| General disorder                                      |                   |                   |  |
| subjects affected / exposed                           | 2 / 16 (12.50%)   | 1 / 14 (7.14%)    |  |
| occurrences (all)                                     | 2                 | 1                 |  |
| Gastrointestinal disorders                            |                   |                   |  |
| Gastrointestinal disorder                             |                   |                   |  |
| subjects affected / exposed                           | 4 / 16 (25.00%)   | 1 / 14 (7.14%)    |  |
| occurrences (all)                                     | 4                 | 1                 |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |  |

|  |                       |                      |  |
|--|-----------------------|----------------------|--|
| Respiratory system disorder<br>subjects affected / exposed<br>occurrences (all)  | 4 / 16 (25.00%)<br>4  | 1 / 14 (7.14%)<br>2  |  |
| Skin and subcutaneous tissue disorders<br>Dermatologic system disorders<br>subjects affected / exposed<br>occurrences (all)            | 4 / 16 (25.00%)<br>6  | 3 / 14 (21.43%)<br>3 |  |
| Psychiatric disorders<br>Psychiatric disorders<br>subjects affected / exposed<br>occurrences (all)                                     | 5 / 16 (31.25%)<br>13 | 7 / 14 (50.00%)<br>7 |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal system disorder<br>subjects affected / exposed<br>occurrences (all) | 4 / 16 (25.00%)<br>4  | 2 / 14 (14.29%)<br>4 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 17 October 2013 | <p>Protocol version 3.0</p> <p>Endpoint outcome measures - added Effect on neurocognitive functions as assessed by the judgement of line orientation task and paired associate learning task.</p> <p>First trial visit (week 0) - added Cognitive functions will be assessed using the following neurocognitive measures: Judgement of line orientation task and paired associate learning task (20 minutes), removed genotyping, added Participants will be given stickers to positively reinforce the successful completion of the task. They will also be given a token of appreciation for their time and effort on the trial.</p> <p>Treatment procedures at 4 week visit - added genotyping, removed mononuclear PMAPKinase activity</p> <p>Trial treatment endpoint at 12 weeks - added Behavioural phenotype measures, Blood tests plasma lipids, liver function tests, renal function tests and creatine kinase, mononuclear PMAPKinase activity, Participants will be given a token of appreciation for their time and effort on the trial.</p> <p>Measuring trial endpoints - added Cognitive symptoms (baseline and 12 week end point) Assessed using the judgement of line orientation task, paired associate learning task.</p> <p>Data Collection - added Participants' cognitive functions will be assessed using the judgement of line orientation task and paired associate learning task and this will be recorded in the case record form.</p> |
| 30 May 2014     | <p>Protocol version 4.0</p> <p>Amendment to patient recruitment age range, from 5-8 years to 4.5- 10.5 years.</p> <p>Cognitive assessment measures added at baseline and 12 weeks (Judgement of line orientation task &amp; Paired associates learning task)</p> <p>Procedure for imaging - If it deemed appropriate, due to difficulties in week 0, the participant may require part of the scan or the entire scan to be performed at week 4.</p> <p>4 week visit (+/- 7 days) - If required brain imaging will be undertaken on the MRI scanner at the CRF without contrast injections or sedation, with support from CRF staff, nursing and play specialists (e.g. if scan at week 0 was incomplete or inadequate)</p>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported