



Clinical trial results:

A phase II double-blind, randomised, placebo-controlled trial of neuroprotection with phenytoin in acute optic neuritis

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-003475-11 |
| Trial protocol | GB |
| Global end of trial date | 06 December 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 30 April 2016 |
| First version publication date | 30 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | UCL/11/0083 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01451593 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University College London |
| Sponsor organisation address | Gower Street, London, United Kingdom, |
| Public contact | CTIMPs , University College London (UCL), 0044 020 7679 6802, ctimps@ucl.ac.uk |
| Scientific contact | CTIMPs, University College London (UCL), 0044 020 7679 6802, ctimps@ucl.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 December 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

In optic neuritis, there is inflammation of the optic nerve, which carries visual information from the eye into the brain. People with optic neuritis lose vision in the eye affected by the disorder, and vision may not recover fully.

Current therapy for optic neuritis can lead to a faster recovery of vision, but does not improve the extent to which vision would recover eventually without treatment. Recent work suggests that loss of vision is due to damage to the nerve fibres in the optic nerve (which is accompanied by damage to the nerve fibres in the retina), that the damage is secondary to a buildup of sodium in these fibres, and that it can be prevented by blocking the entry of sodium into them.

In this clinical trial, the principal objective is to assess whether immediate and sustained blockade of the entry of sodium into nerve fibres with the drug phenytoin protects nerve fibres in the retina and optic nerve from degeneration after an attack of optic neuritis.

Protection of trial subjects:

Full blood count, urea, electrolytes, liver function tests were taken at the screening visit and each subsequent visit to ensure safety. Urine pregnancy test and ECG were also performed at the screening visit to ensure there was no contraindication to phenytoin. Aqua porin 4 antibodies were also taken at the the screening visit and patients found to be seropositive withdrawn from the trial. Participants were assessed clinically by a treating physician at 1, 3 and 6 months from baseline to assess safety

Background therapy:

Concurrent treatment with glatiramer acetate or interferon beta was permitted and corticosteroids for acute optic neuritis could be given at the treating physician's discretion (all participants were offered equivalent regimens of methylprednisolone, either 1 g intravenously daily for 3 days, or 500 mg orally daily for 5 days).

Evidence for comparator:

Corticosteroids hasten recovery after optic neuritis without affecting the final prognosis for recovery. Also previous studies show that corticosteroids do not prevent atrophy of the RNFL or optic nerve, nor visual recovery after optic neuritis and immunomodulation has so far had limited effects on progressive disability. Currently there are no treatments that affect outcome after optic neuritis or other MS relapses. Hence, neuroprotection for both processes contributing to axonal loss and disability remains a key unmet need in optic neuritis and MS.

The anterior visual system has many advantages for testing neuroprotection in MS: acute demyelinating optic neuritis (AON) is a common and often presenting manifestation of MS; the inflammatory optic nerve lesion is comparable to plaques found elsewhere in the central nervous system; and the visual system can be studied using clinical, electrophysiological and imaging techniques. In addition, the optic nerve lesion leads to retrograde degeneration of the retinal nerve fibre layer (RNFL), a relatively pure compartment of unmyelinated axons whose thickness can be measured sensitively and non-invasively using optical coherence tomography (OCT). Therefore, the RNFL thickness provides a plausible biomarker of axonal loss. Reduction of RNFL thickness also corresponds with visual loss in AON and with changes of disability in MS, suggesting that it may provide information on treatment response that is also clinically relevant.

| | |
|---|-----------------|
| Actual start date of recruitment | 03 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 92 |
| Worldwide total number of subjects | 92 |
| EEA total number of subjects | 92 |

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) | 92 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between Feb 3, 2012, and May 22, 2014, and we performed the final assessments in December, 2014

Patients were recruited from one two trial centres in London and Sheffield, UK, or were referred there from a UK network of patient identification centres,

Pre-assignment

Screening details:

Patients were eligible if they were aged 18–60 years, had a clinical diagnosis of unilateral acute demyelinating optic neuritis with no alternative pathological abnormalities on OCT at presentation), visual acuity of 6/9 or worse, and an interval of 14 days or less between onset of vision loss and randomisation

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 92 |
| Number of subjects completed | 86 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-----------------------|
| Reason: Number of subjects | Physician decision: 6 |
|----------------------------|-----------------------|

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, Assessor |

Blinding implementation details:

Participants were randomly assigned (1:1) to phenytoin or placebo via an online randomisation service. Participants were allocated a randomisation code by the treating physician, which was matched to a confidential treatment list by the study pharmacist to assign participants either to phenytoin or placebo (which were identical in appearance). Only the pharmacist was aware of treatment allocation. Treating and assessing physicians and participants were masked to treatment allocation.

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | Active |

Arm description:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

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

Dosage and administration details:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal

doses (each rounded up to the nearest 50 mg) for a period of 3 days

A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

| | |
|---|----------|
| Arm title | Placebo |
| Arm description: | |
| Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient | |
| 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:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

| Number of subjects in period 1^[1] | Active | Placebo |
|---|--------|---------|
| Started | 42 | 44 |
| Completed | 39 | 42 |
| Not completed | 3 | 2 |
| Lost to follow-up | 3 | 2 |

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: 92 patients were initially enrolled into the trial but 6 patients were subsequently withdrawn after entry into the trial due to alternative diagnoses - this is the reason for this discrepancy

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Active |
|-----------------------|--------|

Reporting group description:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

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

Reporting group description:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

| Reporting group values | Active | Placebo | Total |
|---|--------|---------|-------|
| Number of subjects | 42 | 44 | 86 |
| Age categorical 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 33 | 35 | |
| standard deviation | ± 8.2 | ± 9.1 | - |
| Gender categorical Units: Subjects | | | |
| Female | 31 | 32 | 63 |
| Male | 11 | 12 | 23 |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | Active |
| Reporting group description: Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic. | |
| Reporting group title | Placebo |
| Reporting group description: Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient | |

Primary: Active-placebo difference in mean 6 month RNFL thickness adjusted for the baseline RNFL thickness of the unaffected eye

| | |
|--|---|
| End point title | Active-placebo difference in mean 6 month RNFL thickness adjusted for the baseline RNFL thickness of the unaffected eye |
| End point description: High resolution spectral domain OCT images (Spectralis, software version 5.4B, Heidelberg Engineering, Heidelberg, Germany) were acquired at baseline and 6 months using identical protocols at both sites. RNFL measurements used a 3.45 mm diameter circle scan. | |
| End point type | Primary |
| End point timeframe: Mean RNFL thickness was measured at baseline and at 6 months | |

| End point values | Active | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 42 | | |
| Units: microns | | | | |
| arithmetic mean (standard deviation) | 81.46 (± 16.27) | 74.29 (± 15.14) | | |

Statistical analyses

| | |
|--|--------------------------|
| Statistical analysis title | Primary outcome analysis |
| Statistical analysis description: We used an ANCOVA analysis method, using multiple linear regression of the 6-month RNFL of the affected eye on a trial arm indicator with the following prespecified covariates: baseline RNFL thickness in the fellow eye, centre (binary), days between onset and baseline assessment, and whether the participant was prescribed corticosteroids at the time of baseline assessment (no vs 1–5 days before assessment vs 6–30 days before assessment). | |
| Comparison groups | Active v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | ≤ 0.05 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Notes:

[1] - The trial was powered to detect a treatment effect of 50% at a 5% significance level at 80% power while allowing for a 20% combined rate of loss to follow-up and non-adherence.

[2] - Statistical significance, where referred to, indicates a p value of less than 0.05, and all p values refer to two-tailed tests. When regression residuals showed signs of non- normality or heteroscedasticity, we checked p values using a permutation te

Secondary: Active-placebo difference in mean 6 month logMAR visual acuity adjusted for the baseline measurement in the unaffected eye

| | |
|-----------------|--|
| End point title | Active-placebo difference in mean 6 month logMAR visual acuity adjusted for the baseline measurement in the unaffected eye |
|-----------------|--|

End point description:

Best corrected high-contrast logMAR visual acuity was measured using retro-illuminated Early Treatment Diabetic Retinopathy Study charts at 4 m. When no letters could be correctly identified, a score of 1.7 was assigned by the masked researcher.

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

End point timeframe:

Best corrected logMAR visual acuity was measured at baseline and 6 months

| End point values | Active | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 42 | | |
| Units: logMAR | | | | |
| arithmetic mean (standard deviation) | 0.09 (± 0.4) | 0.04 (± 0.18) | | |

Statistical analyses

| | |
|----------------------------|---------------------|
| Statistical analysis title | Secondary endpoints |
|----------------------------|---------------------|

Statistical analysis description:

We analysed secondary outcomes in the same way as the primary outcome measure using the corresponding baseline fellow-eye value of the outcome and the same prespecified covariates.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Active |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | ≤ 0.05 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Notes:

[3] - The trial was powered to detect a treatment effect of 50% at a 5% significance level at 80% power for the primary outcome measure while allowing for a 20% combined rate of loss to follow-up and non-adherence. The trial was not powered to detect treatment effects in the secondary outcome measures

Secondary: Active-placebo difference in mean 6 month low contrast letter score (2.5%) adjusted for the baseline measurement in the unaffected eye

| | |
|-----------------|--|
| End point title | Active-placebo difference in mean 6 month low contrast letter score (2.5%) adjusted for the baseline measurement in the unaffected eye |
|-----------------|--|

End point description:

low-contrast letter scores were measured at baseline and 6 months using retro-illuminated 1.25% and 2.5% Sloan charts (Precision Vision, La Salle, IL, USA) using best refractive correction for each eye at 2 m.

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

End point timeframe:

Low contrast letters scores at both 1.25% and 2.5% were measured at baseline and 6 months

| End point values | Active | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 42 | | |
| Units: low contrast letter score | | | | |
| arithmetic mean (standard deviation) | 19.69 (± 13.8) | 17.55 (± 14.19) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | Secondary endpoints |
|-----------------------------------|---------------------|

Statistical analysis description:

We analysed secondary outcomes in the same way as the primary outcome measure using the corresponding baseline fellow-eye value of the outcome and the same prespecified covariates.

| | |
|---|--------------------------------|
| Comparison groups | Active v Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Secondary: Active-placebo difference in mean 6 month FM-Hue 100 error score adjusted for the baseline measurement in the unaffected eye

| | |
|-----------------|--|
| End point title | Active-placebo difference in mean 6 month FM-Hue 100 error score adjusted for the baseline measurement in the unaffected eye |
|-----------------|--|

End point description:

Colour vision was assessed by masked researchers using the Farnsworth-Munsell 100 hue test and recorded as the total error score. This test was assessed under standard daylight conditions using daylight linear full-spectrum bulbs with a colour temperature of 6500 K in participants with a logMAR visual acuity better than 1.0.

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

End point timeframe:

FM-Huee 100 error score was measured at baseline and 6 months

| End point values | Active | Placebo | | |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 42 | | |
| Units: FM-Hue 100 error score | | | | |
| arithmetic mean (standard deviation) | 181.28 (\pm 223.79) | 195.24 (\pm 212.61) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Secondary outcome analysis |
| Comparison groups | Active v Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Secondary: active-placebo difference in mean total macular volume adjusted for the baseline measurement in the unaffected eye

| | |
|-----------------|--|
| End point title | active-placebo difference in mean total macular volume adjusted for the baseline measurement in the unaffected eye |
|-----------------|--|

End point description:

A fast macular volume scan (20 x20° field, 25 horizontal B scans, ART 9) was performed using a Heidelberg Spectralis machine. Scans were excluded if they had a signal strength of <25 or violated international consensus quality control criteria.

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

End point timeframe:

Macular volume was measured at baseline and 6 months

| End point values | Active | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 42 | | |
| Units: mm3 | | | | |
| arithmetic mean (standard deviation) | 8.25 (\pm 0.45) | 8.07 (\pm 0.42) | | |

Statistical analyses

| Statistical analysis title | Secondary outcome analysis |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

Secondary outcomes were analysed in a similar way to the primary outcome measure, with the corresponding baseline fellow-eye value and the same pre-specified covariates.

| | |
|---|--------------------------------|
| Comparison groups | Active v Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | \leq 0.05 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for the 6 month follow up period

Adverse event reporting additional description:

Adverse events were analysed in all randomised patients including those lost to follow-up.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Active |
|-----------------------|--------|

Reporting group description:

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be sub therapeutic.

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

Reporting group description:

Capsules were over-encapsulated with matching active and placebo capsules to maintain blinding. The placebo capsules contained no active ingredient

| Serious adverse events | Active | Placebo | |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 2 / 44 (4.55%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer female | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 44 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Incidental finding of dilated superior ophthalmic vein seen on MRI | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 44 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |

| | | | |
|--|---|----------------|----------------|
| Congenital malformation | Additional description: Microtia following unplanned conception after randomisation | | |
| | subjects affected / exposed | 0 / 42 (0.00%) | 1 / 44 (2.27%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Appendicitis | | | |
| | subjects affected / exposed | 2 / 42 (4.76%) | 0 / 44 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 2 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Cellulitis | | | |
| | subjects affected / exposed | 0 / 42 (0.00%) | 1 / 44 (2.27%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Severe rash | | | |
| | subjects affected / exposed | 1 / 42 (2.38%) | 0 / 44 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Active | Placebo | |
|---|-----------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 42 (80.95%) | 40 / 44 (90.91%) | |
| Nervous system disorders | | | |
| Headache | | | |
| | subjects affected / exposed | 18 / 42 (42.86%) | 15 / 44 (34.09%) |
| | occurrences (all) | 18 | 15 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| | subjects affected / exposed | 3 / 42 (7.14%) | 17 / 44 (38.64%) |
| | occurrences (all) | 3 | 17 |
| Gastrointestinal disorders | | | |
| Nausea | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 5 | 7 / 44 (15.91%) 7 | |
| Skin and subcutaneous tissue disorders rash subjects affected / exposed occurrences (all) | 8 / 42 (19.05%) 8 | 1 / 44 (2.27%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 22 September 2011 | This amendment was sent as a part of the changes MHRA mentioned in the grounds of Non acceptance. New version of the protocol was submitted to the MHRA. |
| 24 October 2011 | This amendment was done as part of the changes required as per the provisional opinion from the ethics committee. Main study and sub study patient information sheets were modified and sent to the Ethics committee for approvals. |
| 02 July 2012 | Changes were done to Protocol and Patient Information Sheet. Protocol changes include minor changes to the inclusion criteria, schematic diagram of overall trial design, and minor treatment procedures. |
| 09 November 2012 | This amendment was done to reflect the change in the IMP supplier used in the Trial. The license was transferred from Pfizer to Flynn Pharma. This is administrative change and hence the protocol and IMPD were updated and notified to the MHRA |
| 05 June 2013 | The maintenance dose of the study drug was increased from 4mg/kg to 6mg/kg. The protocol has been updated to reflect the change and was notified to the regulatory bodies in the UK. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported