



Clinical trial results:

An Evaluation of the Tolerability and Feasibility of combining 5-Amino-Levulinic Acid (5-ALA) with Carmustine Wafers (Gliadel) in the Surgical Management of Primary Glioblastoma (GALA-5 Trial)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-022496-66 |
| Trial protocol | GB |
| Global end of trial date | 07 March 2014 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 26 October 2016 |
| First version publication date | 26 October 2016 |
| Summary attachment (see zip file) | End of trial report submitted to REC. Publication is being drafted at the time of EMA submission (GALA5 end of trial report.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | UCL/09/0398 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN77105850 |
| ClinicalTrials.gov id (NCT number) | NCT01310868 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University College London |
| Sponsor organisation address | Joint Research Office, Gower Street, London, United Kingdom, WC1E6BT |
| Public contact | Public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk |
| Scientific contact | Scientific contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@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 | 19 January 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 March 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Treatments for patients with glioblastoma are limited. It accounts for around 60% of brain tumours and life expectancy in optimally managed patients is 12-14 months. Treatment options for patients with glioblastoma represents a major unmet need.

To establish that the combined use of 5-ALA and Carmustine wafers is safe and does not compromise a patient from receiving or completing standard chemo-radiotherapy.

Protection of trial subjects:

Patients were closely monitored for site effects following surgery/treatment so they could be treated quickly.

There was a chance patients may have died after surgery following 5-ALA administration and therefore all surgeons using 5-ALA in this trial had to receive training by Medac to minimise this risk.

Treatment for cancer is inherently toxic and like all medication can cause side effects. Many of the anticipated side effects of the two trial drugs were no different to those of other chemotherapy drugs that might be offered to patients off-trial but patients were closely monitored for side effects (including monitoring blood pressure, blood results etc.).

Because 5-ALA should be used in caution in patients with low blood pressure/ cardiac/renal impairment patients with active liver disease, or significant comorbidity precluding radical aggressive therapy were not eligible for the trial. Patients were kept away from UV light sources (e.g windows) for 24 hours after surgery to prevent photosensitivity reactions.

Stopping criteria were in place so that the trial would be recommended to stop if >5% patients failed to start chemoRT due to surgical complications.

Background therapy:

Treatment with temozolomide and RT was to continue as normal based on standard clinical protocols determined by the neuro-oncologist.

For patients which the neuro-oncologists judged to be fit enough, the standard Stupp chemoRT regimen was followed:

- Radiotherapy: 60Gy in 30 fractions (2Gy per fraction given once daily, five days per week (Monday-Friday) over 6 weeks. Radiotherapy delivered to gross tumour volume with 2-3cm margin
 - Concomitant chemotherapy: temozolomide given alongside the radiotherapy at 75mg/m² daily from the first day of radiotherapy, until the last day of radiotherapy, but for no longer than 49 days
 - 4 week break
 - Adjuvant chemotherapy: temozolomide given 150-200mg/m² TMZ 5/28* days for 6 cycles (dosage increase to 200mg/m² on second and subsequent cycles dependent on haematological toxicity. Sites should follow local guidelines if different.). *TMZ to be given on 5 consecutive days followed by 23 days with no TMZ, per cycle.
-

Evidence for comparator:

not applicable - no comparator used

| | |
|---|--------------|
| Actual start date of recruitment | 07 July 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: 72 |
| Worldwide total number of subjects | 72 |
| EEA total number of subjects | 72 |

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) | 54 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Date first site open: 22/06/2011

Date first patient entered: 08/07/2011

Date final patient entered: 05/05/2013

72 patients were recruited across 10 sites in the UK.

Pre-assignment

Screening details:

Screening was performed to confirm eligibility - see reporting group description

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Single arm trial. Blinding not required.

Arms

| | |
|------------------|-----------------------------|
| Arm title | 5-ALA and Carmustine wafers |
|------------------|-----------------------------|

Arm description:

Patients drank up to 20mg/kg of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia.

Carmustine wafers (Gliadel implants) are small discs containing carmustine 7.7mgs (a cytotoxic chemotherapeutic agent) and an inactive ingredient, proliferosan 20. Carmustine implants were inserted (as a single episode) into the cavity left on completion of brain tumour resection. During surgery up to eight discs may have been used to line the resection cavity.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Carmustine Wafers |
| Investigational medicinal product code | L01AD0I |
| Other name | Gliadel |
| Pharmaceutical forms | Implant |
| Routes of administration | Intracerebral use |

Dosage and administration details:

Max 61.6 mg carmustine - i.e. max 8 wafers each containing 7.7mg carmustine plus 192.3mg polifeprosan 20 (excipient) may have been placed in the resection cavity. The number of wafers dispensed depended on clinical judgement.

Oxidised regenerated cellulose (Surgicel) may have been placed over the implants to secure them to the cavity surface. After placement of the implants, the resection cavity should have been irrigated and the dura closed in a water-tight fashion.

| | |
|--|--|
| Investigational medicinal product name | 5-ALA |
| Investigational medicinal product code | |
| Other name | 5-aminolevulinic acid hydrochloride or Gliolan |
| Pharmaceutical forms | Powder for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

The patient drank up to 20mg/kg* of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia - with 5% dose rounding permitted.

| Number of subjects in period 1 | 5-ALA and Carmustine wafers |
|---|-----------------------------|
| Started | 72 |
| Completed | 59 |
| Not completed | 13 |
| Glioblastoma not diagnosed post-operatively | 4 |
| simultaneous diagnosis of unrelated carcinoma | 1 |
| Carmustine wafers not inserted | 8 |

Baseline characteristics

Reporting groups

| Reporting group title | Overall trial |
|-----------------------|---------------|
|-----------------------|---------------|

Reporting group description:

Inclusion criteria

Patient reviewed by MDT and judged fit for treatment

Stealth MRI (neuronavigation) prior to surgery and judged to have typical appearances of a primary GBM

WHO performance status 0 or 1

Age ≥ 18

Exclusion criteria

GBM thought to be transformed low grade or secondary disease

There is uncertainty about the radiological diagnosis

5-ALA or Carmustine wafers is contra-indicated

Pregnant or lactating women

Known or suspected HIV or other significant infection or comorbidity that would preclude radical aggressive therapy for GBM

Active liver disease (ALT or AST $\geq 5 \times$ ULRR)

Concomitant anti-cancer therapy except steroids

History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years

Previous brain surgery (including biopsy) or cranial radiotherapy

Platelets $< 100 \times 10^9/L$

Mini mental status score < 15

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 72 | 72 | |
| 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) | 54 | 54 | |
| From 65-84 years | 18 | 18 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 23 | |
| Male | 49 | 49 | |

End points

End points reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | 5-ALA and Carmustine wafers |
|-----------------------|-----------------------------|

Reporting group description:

Patients drank up to 20mg/kg of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia.

Carmustine wafers (Gliadel implants) are small discs containing carmustine 7.7mgs (a cytotoxic chemotherapeutic agent) and an inactive ingredient, proliferosan 20. Carmustine implants were inserted (as a single episode) into the cavity left on completion of brain tumour resection. During surgery up to eight discs may have been used to line the resection cavity.

Primary: Proportion of 5-ALA resected patients receiving Carmustine wafers

| | |
|-----------------|--|
| End point title | Proportion of 5-ALA resected patients receiving Carmustine wafers ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

% 5-ALA resected patients receiving Carmustine wafers

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: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| End point values | 5-ALA and Carmustine wafers | | | |
|--|-----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 72 ^[2] | | | |
| Units: Patients | | | | |
| 5-ALA resected patients receiving Carmustine wafer | 62 | | | |

Notes:

[2] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with post operative complication

| | |
|-----------------|--|
| End point title | Number of patients with post operative complication ^[3] |
|-----------------|--|

End point description:

Number of patients with a new post-operative deficit or surgical complication (wound infection, CSF leakage, intracranial hypertension)

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

End point timeframe:

post-surgery

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| | | | | |
|-----------------------------|-----------------------------|--|--|--|
| End point values | 5-ALA and Carmustine wafers | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 ^[4] | | | |
| Units: patients | | | | |
| wound infections | 5 | | | |
| cerebrospinal fluid leakage | 4 | | | |

Notes:

[4] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with chemoRT delay

| | |
|-----------------|--|
| End point title | Number of patients with chemoRT delay ^[5] |
|-----------------|--|

End point description:

Number of patients with chemoRT delay (i.e number who do not begin chemoRT 6 weeks after surgery) due to surgical complications.

Standard chemoRT refers to the Stupp regimen as described earlier.

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

End point timeframe:

Following surgery until the beginning of chemoRT

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| | | | | |
|---|-----------------------------|--|--|--|
| End point values | 5-ALA and Carmustine wafers | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 ^[6] | | | |
| Units: patients | | | | |
| wound infections (did not begin chemoRT) | 1 | | | |
| cerebrospinal fluid leakage (did not begin chemoRT) | 1 | | | |
| cerebrospinal fluid leakage (6 week+ delay) | 1 | | | |
| wound infections (6week+ delay) | 3 | | | |

Notes:

[6] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients failing to complete chemoRT without interruption

| | |
|-----------------|--|
| End point title | Number of patients failing to complete chemoRT without interruption ^[7] |
|-----------------|--|

End point description:

Number of patients failing to complete chemoRT without interruption (RT with concomitant chemotherapy, and RT with concomitant plus adjuvant chemotherapy)

Standard chemoRT refers to the Stupp regimen as described earlier.

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

End point timeframe:

Duration of chemoRT

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| End point values | 5-ALA and Carmustine wafers | | | |
|--|-----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 ^[8] | | | |
| Units: patients | | | | |
| concomitant chemo interrupted - toxicity | 13 | | | |
| concomitant RT interrupted - logistical | 9 | | | |
| concomitant RT interrupted - toxicity | 4 | | | |
| adjuvant chemo interrupted - toxicity | 11 | | | |
| adjuvant chemo interrupted - progression | 5 | | | |
| adjuvant chemo interrupted - admin failure | 2 | | | |
| adjuvant chemo interrupted - unknown | 1 | | | |

Notes:

[8] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers

| | |
|-----------------|--|
| End point title | Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers ^[9] |
|-----------------|--|

End point description:

Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers (at first post-operative clinic visit)

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

End point timeframe:

Measured at first post-operative clinic visit

Notes:

[9] - 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: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| | | | | |
|--|-----------------------------|--|--|--|
| End point values | 5-ALA and Carmustine wafers | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 ^[10] | | | |
| Units: patients | | | | |
| same or improved WHO performance status category | 31 | | | |
| lower WHO status post-surgery - 1 category | 21 | | | |
| lower WHO status post-surgery- at least 1 category | 6 | | | |
| not known | 2 | | | |

Notes:

[10] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients failing to start chemoRT due to surgical complications

| | |
|-----------------|---|
| End point title | Number of patients failing to start chemoRT due to surgical complications ^[11] |
|-----------------|---|

End point description:

Number of patients failing to start chemoRT due to surgical complications.

Standard chemoRT refers to the Stupp regimen as described earlier.

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

End point timeframe:

Post-surgery until decision to not administer chemoRT

Notes:

[11] - 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: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

| | | | | |
|-----------------------------|-----------------------------|--|--|--|
| End point values | 5-ALA and Carmustine wafers | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 ^[12] | | | |
| Units: patients | | | | |
| cerebrospinal fluid leakage | 1 | | | |
| wound infection | 1 | | | |

Notes:

[12] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred between informed consent and 8 weeks post surgery or the end of all radiotherapy and concomitant and adjuvant chemotherapy, whichever is later (or after this date if the site investigator felt the event was trial treatment related)

Adverse event reporting additional description:

As per publication, AEs have only been reported for the 59 eligible patients. SAEs are listed in full. Non-serious adverse events includes all events (including SAEs) of grade 3 or higher with a 5% threshold frequency.

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

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | All eligible patients (59) |
|-----------------------|----------------------------|

Reporting group description:

Patients received up to 20mg/kg 5-ALA prior to surgery and up to 8 carmustine wafers inserted into the resected cavity.

| Serious adverse events | All eligible patients (59) | | |
|---|----------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 59 (44.07%) | | |
| number of deaths (all causes) | 49 | | |
| number of deaths resulting from adverse events | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Wound dehiscence | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hematoma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thromboembolic event | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 59 (5.08%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrospinal Fluid Leak | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 59 (13.56%) | | |
| occurrences causally related to treatment / all | 9 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stroke | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasovagal Reaction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colonic Perforation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| other - bowel perforation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intra-abdominal hemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary Edema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Psychiatric Disorders- other | | | |
| Additional description: steroid induced aggression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle weakness left sided | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infection - Cerebral Abscess | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections - other | | | |
| Additional description: not otherwise specified | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |

| | | | |
|---|----------------|--|--|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Urinary tract infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | All eligible patients (59) | | |
|---|----------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 59 (38.98%) | | |
| Investigations | | | |
| Neutrophil Count Decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | | |
| occurrences (all) | 4 | | |
| Platelet count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | | |
| occurrences (all) | 4 | | |
| White blood cell decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | | |
| occurrences (all) | 3 | | |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|--|--|
| <p>complications</p> <p>Wound infection</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 59 (5.08%)</p> <p>3</p> | | |
| <p>Vascular disorders</p> <p>Thrombolytic event</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 59 (6.78%)</p> <p>4</p> | | |
| <p>Nervous system disorders</p> <p>Seizure</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lethargy</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 59 (8.47%)</p> <p>5</p> <p>3 / 59 (5.08%)</p> <p>3</p> | | |
| <p>Gastrointestinal disorders</p> <p>Nausea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 59 (6.78%)</p> <p>4</p> <p>3 / 59 (5.08%)</p> <p>3</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Muscle weakness</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 59 (8.47%)</p> <p>5</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 10 February 2011 | Response to REC comments: Protocol v2.0 with minor amendments & statistics section updated, Amended PIS v2.0 and consent form v2.0 as per RECs comments, IRAS form questions regarding loss of capacity answered |
| 22 February 2011 | Amendment to site IMP labelling requirements to meet Annex 13 clause 32 |
| 25 May 2011 | Change to IRAS filter question 7 (capacity to consent) in response to change to the IRAS wording. |
| 24 June 2011 | Protocol v3.0. Amendment to Pregnant Partner Information Sheet & ICF. New document: Pregnant Patient Information Sheet & ICF. |
| 14 February 2012 | 5.1 MRI no longer ideally to be conducted on either no or stable steroids 5.1. MRI registration assessment date extended from 2 to 4 weeks. The MRI scan date given must correspond to the scan discussed at a recent MDT meeting from which a provisional diagnosis has been made. 5.3.1. Clarification that Stealth MRI (neuronavigation) will be performed prior to surgery. |

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.

-non-serious AEs: 'occurrences all number' cannot be provided as only highest grade experienced by patients collected on CRF; subjects affected number is entered instead
-serious AEs & non-serious AEs are listed under non-serious adverse event.

Notes: