END OF STUDY SUMMARY CLINICAL STUDY REPORT

A double-blind randomised controlled trial of Lithium Carbonate in patients with Amyotrophic Lateral Sclerosis (LiCALS)

EudraCT number: 2008-006891-31 **Sponsor Protocol Number: RAA/2008/013**

King's College London Institute of Psychiatry
P.O Box 01
De Crespigny Park
London
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Study initiation Date: 4 June 2009

Study Completion Date: 30 April 2012

Report Date: draft1, 8 April 2014

Chief Investigator: Professor Ammar Al-Chalabi

This study was performed in accordance with the principal of Good Clinical Practice

APPROVALS

Report Title: A double-blind randomised controlled trial of Lithium Carbonate in patients with Amyotrophic Lateral Sclerosis (LiCALS)

Report Authors: Mrs Marie Thornhill
Dr Nick Steen
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The final summary report as been approved by

Professor Ammar Al- Chalabi

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Report Authors: Mrs Marie Thornhill
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Dr Christine Payan
Professor John Zajicek
Dr Brian Dickie (MND Associate Observer)

Data Monitoring & Ethics Committee

Dr Carl Counsell (Chair August 2011 to April 2012)
Dr Chris Allen (Chair December 2008 to August 2011)
Dr Amanda Farrin

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ALT	Alanine aminotransferase
AR	Adverse Reaction
BDNF	Brain derived neurotrophic factor
DeNDRoN	The Dementias & Neurodegenerative Diseases Research Network
DMEC	Data Monitoring & Ethics Committee
EQ-5D	EuroQol Questionnaire
EMG	Electromyography
GCP	Good Clinical Practice
GSK3β	Glycogen kinase synthase 3 Beta
HADS	Hospital Anxiety & Depression scale
IMP	Investigational Medicinal Product
JCTO	Joint Clinical Trials Offices
LiCO3	Lithium Carbonate
MHRA	Medicines & Healthcare products Regulatory Agency
MAPT	Microtubule-associated protein tau
MH&N CTU	Mental Health and Neurosciences CTU, Institute of Psychiatry Clinical Trials Unit, King's College London
MND	Motor Neurone Disease
MRIS	Medical Research Information Service
MRC	Medical Research Council
mTOR	Mammalian target of rapamycin
NCTU	Newcastle Clinical Trials Unit

NICE	National Institute for Clinical Excellence
NMDA	N-methyl-D-aspartic acid
NRES	National Research Ethics Service
NR2B	NMDA receptor subtype 2B
PI	Phosphoinositol/Principal Investigator depending on context
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SVC	Slow Vital Capacity
SOP	Standard Operating Procedure
SOD 1	Superoxide dismutase
SPC / SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFT	Thyroid function test
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRN	UK Clinical Research Network

1.0 Summary

Trial ID	**EudraCT Number:** 2008-006891-31
Phase	IV
Country	UK
Protocol Title	A double-blind randomised controlled trial of Lithium Carbonate in patients with Amyotrophic Lateral Sclerosis (LiCALS)
Trial Design	Multi-centre double-blind randomised parallel group controlled trial with Open Label Extension.
Dosing Regimen	Lithium Carbonate (or Lithium Citrate for Open Label Extension PEG patients)
Study Population	Participants aged >18-yrs, male or female with possible, laboratory-supported probable, probable or definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria
First Patient First Visit	26 May 2009
Last Patient Last Visit	7 November 2011
Planned Enrolment	220
Subject Exposure	214

2.0 Title

A double-blind randomised controlled trial of Lithium Carbonate in participants with Amyotrophic Lateral Sclerosis (LiCALS).

LICALS is a double-blind randomised controlled trial of lithium carbonate in participants with Amyotrophic Lateral Sclerosis. This study is investigating lithium carbonate at varying doses, aiming to achieve blood levels of 0.4-0.8 mmol/L).

3.0 Investigators and Study Centres

LICALS was conducted across 10 UK MND care centres; Professor Karen Morrison (01. Queen Elizabeth Hospital, Birmingham), Professor Ammar Al- Chalabi – formerly Professor Nigel Leigh (02. King's College, London), Professor Carolyn Young (03. The Walton Centre, Liverpool), Dr John Ealing (04. Salford Royal Hospital, Manchester), Dr Richard Orrell (05. The National Hospital for Neurology, London), Dr Tim Williams (06. Newcastle General Hospital, Newcastle), Dr Kevin Talbot (07. John Radcliffe Hospital, Oxford), Professor Oliver Hanemann (08, Royal Derriford Hospital, Plymouth), Dr Tahir Majeed formerly Professor Douglas Mitchell (09. Royal Lancaster Hospital, Preston), and Professor Pamela Shaw (Royal Hallamshire Hospital, 10. Sheffield).

Recruitment to the double blind phase ran from 4 June 2009 to 30 April 2010 and the Open label extension (OLE) 4 December 2010 to 30 November 2011.

The data included in this report was generated and assessed between 4 June 2009 to 30 March 2012 and focuses on the findings of the double blind phase only. The trial remained open throughout this period. All the above-mentioned sites recruited and monitored participants during this time.

4.0 Publications

Al-Chalabi A, Shaw PJ, Young CA, Morrison KE, Murphy C, Thornhill M, Kelly J, Steen IN, Leigh PN, UKMND-LiCALS; Protocol for a double-blind randomised placebo-controlled trial of Lithium Carbonate in patients with Amyotrophic Lateral Sclerosis (LiCALS). BMC Neurology 2011, 11:111

Al-Chalabi A, Shaw PJ, Young CA, Morrison KE, Murphy C, Thornhill M, Kelly J, Steen IN, Leigh PN, UKMND-LiCALS; Lithium in patients with amyotrophic lateral sclerosis (LiCALS): a phase 3 multicentre, randomised, double-blind, placebo-controlled trial Lancet Neurol 2013; 12: 339–45

5.0 Study Period

Date first participant on study: 5 June 2009

Date last participant recruited to double blind (DB) phase: 30 April 2010

Date last DB participant completed (off study): 7 November 2011

Two-hundred and twenty participants were expected to be recruited to the trial during a 6 month

period (June 2009 to November 2009). However recruitment slipped due to a number of issues which meant that the trial as a whole had to be extended by a further 5 months (until April 30 2012).

There were 3 possible reasons for the recruitment slippage;

a) Participant Overestimation:

Possibly overestimated the pool of participants available for trials, especially since for two large centres (Sheffield and King's) recruitment for LiCALS coincided with recruitment to the Trophos study- a factor beyond our control.

b) Negative Lithium Publicity

By the time we opened recruitment there had been a significant negative rebound in the mood amongst participants with MND concerning lithium (for example, in discussions on the Patients-Like-Me website) and this became more evident and widespread when in the summer of 2009 the news broke about the cessation of the North American Lithium study, and at the end of the year, the halting of the Italian trial. Having urgently discussed the data available to us from these studies with our Trial Steering Committee (TSC), with the Independent Data Monitoring and Ethics Committee (DMEC), and with the Principal Investigators, The Trial Management Group took immediate and vigorous action, in conjunction with the Motor Neurone Disease Association (MND), to reassure participants with MND in the UK that (in our view) there were no significant safety concerns, and that LiCALS should continue.

In order to rectify this situation, at King's we reviewed recruitment weekly, regularly encouraged centres to search for new candidates, circulated monthly figures to all Centres, and dealt promptly to resolve any queries about recruitment in individual cases. In addition, from an early stage we worked with the MND Association to improve the access to information about LiCALS on their website, and to broadcast the need for more recruits through the RCDA network. We also circulated all UK neurologists with information about the trial through the Association of British Neurologists (ABN) monthly newsletter.

c) Competing Trials / Participants

Finally, it is relevant that even the Trophos (Mitotarget) study, which our feedback indicated was inherently more attractive to patients, had to extend the period of recruitment. The Trial Management Group concluded that although recruitment was slower than hoped the two-hundred and fourteen participants recruited was sufficient to power the study.

6.0 Objectives

6.1 Primary Objective:

- To determine whether lithium carbonate ($LiCO_3$), in doses achieving blood levels of 0.4-0.8 mmols/L, combined with standard ALS treatment, significantly prolongs survival in ALS over 18 months, compared with standard treatment alone.

6.2 Secondary Objectives:

- To monitor the safety of treatment with $LiCO_3$ over 18 months.
- To determine whether treatment with $LiCO_3$ slows the rate of functional deterioration over 18 months.
- To determine whether treatment with $LiCO_3$ affects quality of life (QoL) or mental state (anxiety, depression) in participants with ALS, over 18 months.

These objectives remained the same for the duration of the trial.

7.0 Regulatory Status

LiCALS was conducted under Clinical Trial Authorisation 14523/0217-001) and ISRCTN83178718.

The study and all amendments were reviewed by an independent ethics committee: the NRES Committee London- South East (formerly known as the South East Research Ethics Committee. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

The following substantial protocol amendments were made:

Substantial amendment 01 Approved 20 May 2009
Ethics (MHRA for information only)

Reasons for amendment:

- To correct the e mail contact details for the Chief Investigator
- To specify a blood test for trial medication levels at baseline
- To define the blood tests that will be used to monitor safety
- To specify that a physician is responsible for doing the neurological exam pre-randomisation
- To clarify the arrangements for Lithium (unblinded) and treating (blinded) physicians
- To insert a document history as an appendix.
- MHRA was notified that the person responsible for QP release had changed - that's been sub-contracted to Dr Peter Vogel. The original CTA application lists the site where the QP

certifies batch release as Haupt-Pharma Brackenheim GmBH, and that hasn't changed. The responsibility for QP release remains with Haupt-Pharma Brackenheim GmBH.

Substantial amendment 02 Approved 6 October 2009

Ethics (MHRA for information only)

Reasons for amendment:

- Clarification of haematological markers
- To clarify when safety (lithium) blood tests are to be drawn.
- Update the contact details at the Joint Clinical Trial Office, who has taken on the Sponsor's safety reporting responsibilities to the MHRA.
- Amendment of contact details for Sponsor contact. This is now Ms Jackie Pullen rather than Professor Peter McGuffin
- To include new information in the PIS and protocol about the USA and Canada announced on 23rd September 2009 that a North American trial of lithium carbonate in people with ALS/MND would stop early and that is no significant concerns with regards the safety of LiCALS.
- To seek approval for a standard cover letter to go to all patients along with the PIS explaining the situation with the US/Canadian study as it is felt inappropriate to send the revised PIS out 'cold' without an explanatory cover letter.

Substantial amendment 03 Approved 31st December 2009

Ethics (MHRA for information only)

Reasons for the amendment:

- Extend LICALS recruitment timelines by 4 months (to March 2010)
- Closure of Italian Lithium Trial; TSC/ DMEC had no safety concerns on review of the LICALS data and unanimously agree that the trial remain open.

Substantial amendment 04 Dated 6th May 2010, Approved 22nd June 2010

Ethics (MHRA for information only)

Reasons for the amendment:

- Change in legal representative Professor Peter McGuffin to Professor Shitij Kapur.
- To detail changes to Chief Investigator personnel, of the open label extension and inform details of recruitment extension from 31st March 2010 and 30th April 2010.
- To inform you of the transfer of Chief Investigator duties and responsibilities from Professor Nigel Leigh to Professor Ammar Al-Chalabi as of 01 July 2010.
- To extend recruitment for the double blind section of the study from 31st March 2010 to 30th April 2010.

- Decreasing the frequency of pregnancy tests in the double blind study.
- Detail the procedures and assessments of the open label extension study.

Substantial amendment 05 Dated 2nd August 2010, Approved 29 Nov 2010
Submitted to Ethics and MHRA

Reasons for the amendment:

- To include lithium citrate formulation for PEG patients
- To clarifying dosing regime
- Reduce the open label the timelines from month 18 to month 15; starting in Dec 2010 and closing March 2012.
- To change the primary analysis method for the double blind i.e. from Fisher's Exact to Kaplan Meier.
- Include open label patient information sheet version 1, 2nd August 2010.

Amendment 6 - Non-substantial 01, Approved 3 February 2011
Ethics only; Protocol version 8, dated 14 December 2010

Reasons for the amendment:

- To inform the Ethic of the deputising of Dr Tahir Majeed at the Preston site.
- Administrational changes to OLE assessment scheduled; ECGs and pregnancy test to reflect in the visit schedule.

The study was based in the UK, in partnership with the Motor Neurone Disease (MND) Association and Dementias & Neurodegenerative Diseases Research Network (DeNDRoN). The Study was funded by the MND association and monitored by Kings' College Institute of Psychiatry (KCL IOP). The study was managed and conducted in accordance with the Principles of Good Clinical Practice and with the KCL IOP, Mental Health and Neurosciences Clinical Trials Unit (MH&N CTU) and the Joint Clinical Trials Office (JCTO) Standard Operation Procedures (SOPs).

8.0 Study Design

The LiCALS double blind study which is the subject of this report was a multi-centre (UK) double-blind randomised parallel group controlled trial to evaluate the efficacy, safety, and tolerability of lithium carbonate ($LiCO_3$) at doses to achieve stable 'therapeutic' plasma levels (0.4-0.8 mmol/L), plus standard treatment, versus matched placebo plus standard treatment.

All participants were required to be taking standard treatment for ALS (riluzole 100 mg daily) as per routine clinical practice for at least 28 days (four weeks) prior to screening.

Patients were identified through clinics at each of the 10 centres, which are all MND care centres. They were given the patient information sheet to read, and will have 7-14 days to decide whether

to participate in the study. At clinic, there was opportunity for the participants to ask questions of a member of staff trained in all trial procedures, as delegated by the PI. The Principal Investigator at each site will ensure that the participants meet the inclusion and exclusion criteria at the point of screening.

After signing the consent form, participants had blood tests to measure their thyroid function, detect any renal and hepatic insufficiency, any haematological, biochemical or immunological abnormalities, and their SVC will be measured. If they are a woman of childbearing potential, they will have a urine pregnancy test at each of their clinic visits. Those procedures were done within 1 month prior to randomisation.

A screening log was kept at site to document details of patients invited to participate in the study. For patients who decline or are ineligible, this will document any reasons available for non-participation (where provided). The log ensured potential participants are only approached once.

The original signed consent form was retained in the Investigator Site File, with a copy in the participant's hospital medical notes, and a copy provided to the participant. Participants specifically consented to their GP being informed of their participation in the study (see Appendix 5 for a copy of the template participant information sheet and consent form).

Patient identification numbers were allocated by registering the patient on the MACRO eCRF system, after consent has been signed. The system will generate a unique identifier to be used throughout the study.

The PIN were a five digit number; the initial two digits indicate the centre

(Birmingham = 01; King's College Hospital = 02; Liverpool = 03; Manchester = 04; National Hospital for Neurology and Neurosurgery = 05; Newcastle = 06; Oxford = 07; Plymouth = 08; Preston = 09; Sheffield = 10), and then a three-digit number indicating the number within the centre.

Consenting participants were randomised by site to a 1:1 ratio of oral 295mg Lithium carbonate (LiCO3) plus standard treatment or matched placebo plus standard treatment for the duration of the treatment period (77 weeks). Randomisations were completed using the online system based at the Mental Health & Neuroscience Clinical Trials Unit (MH&N CTU) based at the Institute of Psychiatry.

Allocation was stratified by centre and site of disease onset, by stratified block randomisation with randomly varying block sizes.

Only site staff authorised to request randomisation will be sent passwords for the randomisation

system. Requests for passwords are via the trial manager to the MH&N CTU.

A total of 220 patients was initially planned to be recruited to power the study.

Assignment to either lithium carbonate or placebo was blinded to the participants, investigators and pharmacy (double-blind). Blinding of patients and treating physicians to allocation status will be assured by identical tablet appearance, by identical labelling between placebo and doses of active drug, and by sham dosage adjustments made by a lithium physician (unblinded) in the control group to mirror titration of lithium dosage in the intervention group. For safety reasons, lithium physicians (unblinded) will monitor plasma lithium levels, safety bloods, and symptoms. Every effort was made to maintain strict blinding, although for practical reasons, the un-blinded lithium physicians was part of the same unit as the treating physicians (blinded). A separate database held details linked to lithium monitoring in which lithium physicians (unblinded) had 24 hrs after being made aware of results to enter data. Details of how the blinding will be maintained are given in Flow Diagram 1.

A set of sealed code-break envelopes will be prepared by Haupt Pharma and sent to Guy's Medical Toxicology Unit; these envelopes should be opened only where knowledge of the randomised treatment is needed to optimise the clinical management of the patient. Code breaks was not be routinely opened for participants who complete study treatment.

A sealed randomisation list was also be held by MH&N CTU as back-up.

If a request for code break is received from a physician (e.g. the patient's general practitioner) outside the research team, Guy's Medical Toxicology Unit will attempt to contact the research team to verify the request before the code is broken.

If the code is broken, details including patient study number, the date code break was performed, the person who broke the code, and reason for code break shall be recorded on a record card within the code break envelope and maintained. If clinically indicated, the participant was withdrawn from study medication.

Accidental unblindings will be dealt with on a case by case basis, if and when they arise. Research staff continued to collect the patient's data according to the visit schedule, unless the patient withdrew their consent.

The following visit assessment schedule was adhere to:

TABLE 1: VISIT ASSESSMENT SCHEDULE

Phase	Pre-Rando	Double-Blind Treatment												
Study Week/month	Wk -4 to Day 0	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Mth 6	Mth 9	Mth 12	Mth 15	Mth 18 /Wk 77	Wdth
Informed	x													
Registration/	x													
SVC	x													
ALS History	x													
ALS	x	x						x	x	x	x	x	x	X
Medical	x													
Neurological	x													
Inclusion/Exc	x	x												
Physical	x	x						x	x	x	x	x	x	X
ALSFRS-R		x						x	x	x	x	x	x	X
EQ-5D		x						x	x	x	x	x	x	X
HADS		x						x	x	x	x	x	x	X
ECG	x								x		x		x	
Haematology	x					X	x	x	x	x	x	x	x	
Biochemistry	x		x	x	x	X	x	x	x	x	x	x	x	
Dose	x[3]	x	x	x	x	X	x	x	x	x	x	x	x	X
Urine	x	x				X	x	x	x	x	x	x	x	X
Thyroid	x								x		x		x	
Concomitant	x	x	x	x	x	X	x	x	x	x	x	x	x	X
Adverse		x	x	x	x	X	x	x	x	x	x	x	x	X
Trial		x				X	x	x	x	x	x	x	x	X
Drug		x				X	x	x	x	x	x	x	x[3]	x[4]
Patient													x	X
Physician													x	X
Withdrawal														X

8.1 Treatment Group

Participants were Age: ≥18 years (inclusive) patients with Possible, Laboratory-supported Probable, Probable or Definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria (The 'Airlie House Statement'; onset form (bulbar or limb) and disease type (familial or sporadic); documented electromyogram (EMG) reported by an experienced neurophysiologist as compatible with ALS. In addition a neurological exam performed by a

physician.

Participants who had disease duration ≥6 months and ≤36 calendar months (inclusive), with disease onset defined as date of first muscle weakness, or dysarthria. Slow vital capacity (SVC) ≥60% of predicted within 1 month prior to randomisation.

8.2 Treatment

"Treatment" was defined as the administration of a single 295mg tablet dose of $LiCO_3$ *plus* standard treatment or placebo *plus* standard treatment.

Tablets were taken once daily, starting with one tablet (295mg daily) initially, titrated up to two or three tablets daily over the first four weeks of treatment, depending on blood lithium levels. Blood levels will be measured at baseline, 7 days (12 hours +/-30 minutes after previous evening dose), and at 14 days (12 hours +/-30 minutes after previous evening dose). The target range for the lithium plasma level will be between ≥0.4 mmol/l and ≤ 0.8 mmol/l. Further plasma level measurements will be taken at 21 and 28 days to confirm the target range has been achieved. Ongoing lithium level monitoring will be scheduled for week 8 and week 12, and 3 monthly thereafter for the duration of the study.

Dose adjustments were made by reducing back to 2 tablets daily or to 1 tablet daily as required. It is anticipated that most patients will remain on 2 tablets throughout the duration of the trial.

Sham dose adjustments were made to patients on placebo to maintain blinding in clinical sites as per SOP.

8.3 Treatment Cessation:

5 day treatment cessation was permitted with the approval of Chief Investigator. Participants who failed to restart treatment within the appointed 5 day period were requested to restart dose titration phase (on a single tablet) to ensure that safety of the participant. In addition comply with a fortnight unscheduled blood monitoring.

9.0 Safety and Efficacy Assessments

Baseline clinical assessments were completed within 28 days prior to the participants starting on the treatment.

Each recruiting site had a team of unblinded personnel to ensure that blood levels remain with 0.4 to 0.8 mmol/l and that any adverse events (AEs) were not attributed to the study drug thus maintaining the safety monitoring of participants.

Blood levels were monitored to the following schedule:

TABLE 2: SAFETY BLOOD TESTS

Phase	Pre-Randomization	Weekly visits						Monthly visits						W/I
Blood test	**Wk -4 to Day 0**	**0**	**1**	**2**	**3**	**4**	**8**	**3**	**6**	**9**	**12**	**15**	**18**	**Withdrawal**
Haematology	x					x	x	x	x	x	x	x	x	
Biochemistry	x		x	x	x	x	x	x	x	x	x	x	x	
Thyroid Function	x								x		x		x	
Li Levels	x	x	x	x	x	x	x	x	x	x	x	x	x	x

The LiCALS Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) reviewed all LICALS SAEs data. Teleconferences are scheduled for every 3 and 6 months respectively.

- Lithium blood levels data was reviewed by the DMEC during the closed meeting. The DMEC are reassured that study medication is being initiated appropriately.
- In November 2009 the LiCALS TSC and DMEC reviewed all LICALS SAEs data following the closure of the North American Lithium Trial (September 2009) and the Italian Trial (October 2009). The Committees subsequently met on both occasions and unanimously agreed that there are no safety issues and that the LiCALS trial should remain open.

9.1 RISK (SmPC)

Contra- Indications

- A history of hypersensitivity to lithium or any of the excipients.
- Severely impaired renal function
- Untreated or untreatable hypothyroidism.
- Cardiac disease associated with rhythm disorder.
- Low body sodium levels for example dehydrated patients, those on low sodium diets, or those with Addison's disease.
- Breast feeding

Pre treatment with Lithium

Prior to commencing treatment with Lithium the following must be evaluated:

- renal function
- Cardiac function
- Thyroid function should be evaluated. Patients should be euthyroid before initiation of lithium therapy.
- Renal, cardiac and thyroid functions should be re-assessed periodically.

Monitoring of blood lithium levels

- Serum concentration of lithium should be measured on a sample taken just prior to the time when a dose of lithium is due to be taken (i.e. at trough level 12 hours following the last dose).
- Toxic effects may be expected at serum-lithium concentrations of about 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously

Warnings to be given to patients about signs and symptoms of toxicity

Clear instructions regarding the symptoms of impending toxicity were given by the doctor to all patients receiving long-term lithium therapy (see Section 4.9 for symptoms of intoxication) and advice given for the need for urgency in seeking medical assistance if these symptoms appear.

Interactions which increase lithium concentrations

Co-administration of the following drugs with lithium may lead to increased lithium concentrations and a risk of toxicity:

- any drug which may cause renal impairment has the potential to cause lithium levels to rise, thereby causing toxicity. If the use of the drug is unavoidable, carefully monitor lithium blood level and adapt dosage as necessary.
- antibiotics (metronidazole, tetracyclines, co-trimoxazole, trimethoprim), N.B. Toxic symptoms may also occur at low or normal levels when used in conjunction with co-trimoxazole or trimethoprim. non-steroidal anti-inflammatory drugs (including selective cyclo-oxygenase (COX) II inhibitors.
- drugs affecting the renin angiotensin system (ACE inhibitors, Angiotensin II receptor antagonists).
- Diuretics (including herbal preparations). In addition to the effects noted above, thiazide diuretics show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication. Loop diuretics (furosemide and bumetanide, seem less likely to cause lithium retention, although caution is warranted.
- Other drugs affecting electrolyte balance, e.g. steroids, may alter lithium excretion and

should therefore be avoided.

Interactions which may not be associated with increased or reduced lithium levels:

- Concomitant use of the following drugs may precipitate symptoms of toxicity when the lithium level is within the normal range.
- antipsychotics, including the atypical antipsychotics olanzapine, clozapine and haloperidol at high doses.
- carbamazepine
- phenytoin
- methyldopa
- clonazepam
- tricyclic and tetracyclic antidepressants
- calcium channel blockers. These drugs may cause neurotoxic reactions at therapeutic levels.
- neuromuscular blocking agents. Lithium may cause neurotoxic reactions at therapeutic lithium levels.
- Selective serotonin re-uptake inhibitors (SSRIs): Concurrent use with lithium may precipitate a serotonergic syndrome.
- Non-steroidal anti-inflammatory drugs including COX II inhibitors: monitor serum lithium concentrations more frequently if NSAID therapy is initiated or discontinued
- Triptans: lithium toxicity reported suggestive of serotonin syndrome.

Drugs which prolong the QT interval

- Lithium can cause an increase in the QTc interval, particularly at higher blood levels. Therefore concurrent use of drugs which have a risk of prolonging the QTc interval should be avoided, and consideration be made of other potential risk factors such as increasing age, female sex, congenital long QT syndrome, cardiac and thyroid disease and the following metabolic disturbances: hypocalcaemia, hypokalaemia, hypomagnesaemia.
- The following products have a high risk of causing QT prolongation and torsade de pointes: Class Ia antiarrhythmics , (disopyramide, procainamide, quinidine), Class III antiarrhythmics (amiodarone, sotalol), arsenic trioxide, artemisinin derivatives, dolasetron mesylate, mefloquine, intravenous erythromycin, amisulpride, haloperidol, pimozide, sertindole, terfenadine, thioridazine.
- ECG should be performed after initiation of treatment and at any point where the patient becomes symptomatic or when there are changes in disease or treatment which may increase the risk of interaction or arrhythmia.

Non Drug Interactions:

- Low sodium diet. Rapid reduction of sodium intake may cause raised lithium levels.
- Intercurrent illness may cause lithium toxicity.
- Raised plasma levels of ADH may occur during treatment

10.0 Diagnosis and Main Criteria for Inclusion / Exclusion

The following inclusion/ exclusion criteria remain throughout the period of the trial.

10.1 Inclusion criteria

1. Patients with Possible, Laboratory-supported Probable, Probable or Definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria (The 'Airlie House Statement': http://www.wfnals.org)

   These criteria are internationally accepted research diagnostic criteria with high specificity and sensitivity. The onset form (bulbar or limb) and disease type (familial or sporadic) will be recorded; source documents will include a full report of an electromyogram (EMG) reported by an experienced neurophysiologist as compatible with ALS. The neurological exam should be performed by a physician.
2. Disease duration ≥6 months and ≤36 calendar months (inclusive), with disease onset defined as date of first muscle weakness, or dysarthria.
3. SVC ≥60% of predicted within 1 month prior to randomisation
4. Age: ≥18 years (inclusive).
5. In the case of a female with childbearing potential, the patient must not be pregnant or breast-feeding. Women of childbearing potential will have a urine pregnancy test before randomisation; and at each clinic visit. The results of those must be negative. Women of childbearing potential should use adequate contraception.
6. Continuously treated with riluzole for at least 4 weeks prior to screening (28 days inclusive) and stabilised at 100 mg/day (50 mg bid) without significant adverse drug reactions.
7. Capable of understanding the information given and giving fully informed consent prior to any study specific procedures.

10.2 Exclusion criteria

1. Participation in another therapeutic study within the preceding 12 weeks or use of other

investigational drugs or agents.

2. Tracheostomy, or assisted ventilation of any type during the preceding three months.
3. Existing gastrostomy, unless elective and not currently used for nutritional support or hydration.
4. Any medical condition known to have an association with motor neuron dysfunction which might confound or obscure the diagnosis of ALS.
5. Presence of any concomitant life-threatening disease or any disease or impairment likely to interfere with functional assessment.
6. Confirmed hepatic insufficiency or abnormal liver function (ALT greater than 1.5 times the upper limit of the normal range) within one month of randomisation. That blood test may be repeated in the case of initial abnormal results; if the levels return to normal, the patient may then be included in the study.
7. Renal insufficiency (serum creatinine ≥ULN for the centre/local laboratory) within one month of randomisation.
8. Recorded diagnosis or evidence of major psychiatric disorder or clinically evident dementia.
9. Known allergy or hypersensitivity to lithium, or its excipients.
10. Likely to be uncooperative or to fail to comply with the trial requirements or to be inaccessible in the event of an emergency.
11. Subjects with significant haematological, biochemical and autoimmune abnormalities, as judged by the study physician.
12. If a woman of childbearing potential, unable or unwilling to use effective contraception during the study.
13. Patients with active inflammation/infection at screening or Baseline (Day 0). Patients presenting with active inflammation/infection can be reassessed at a later date, and included in the trial if the infection/inflammation has cleared.
14. Patients already taking lithium in any form.
15. Presence of a medical condition contra-indicative to the use of lithium, according to the BNF (http://www.bnf.org/bnf/)

11.0 Study Drug

Lithium Apogepha® 295 mg tablets containing lithium carbonate.

Market Authorisation Holder - APOGEPHA Arzneimittel GmbH.

Market Authorisation Number - 3000569.00.00

Matched Placebo – manufactured and QP released by Haupt Pharma Brackenheim GmBH

11.1 Placebo

The placebo was identical in appearance to the active tablets — white tablets of tablets of approximately 1.1 cm in diameter, with a break notch on one side.

11.2 Active medication; Lithium Carbonate

Lithium carbonate is a licensed for the treatment and prophylaxis of mania, bipolar disorder (manic-depressive disorder), recurrent depression, and the control of aggressive or self-mutilating behaviour. Within the context of this study, lithium carbonate were to be used in a new target population.

Active study medication and placebo will be supplied in blisters of 21 tablets. For months 1, 2 and 3, five blisters will be packaged into 1 month kits. 3 of these kits, each bearing the same kit number, was packaged together and dispensed directly to the study site.

Thereafter, 14 individual blisters will be supplied in 3-monthly patient kits for months 4-6, 7-9, 10-12, 13-15 and 16-18. Each of those kits had a different kit number. Packaging and labelling were completed in accordance with Good Manufacturing Practice (GMP) Annex 13 requirements and GCP, by Haupt Pharma, Brackenheim, Germany.

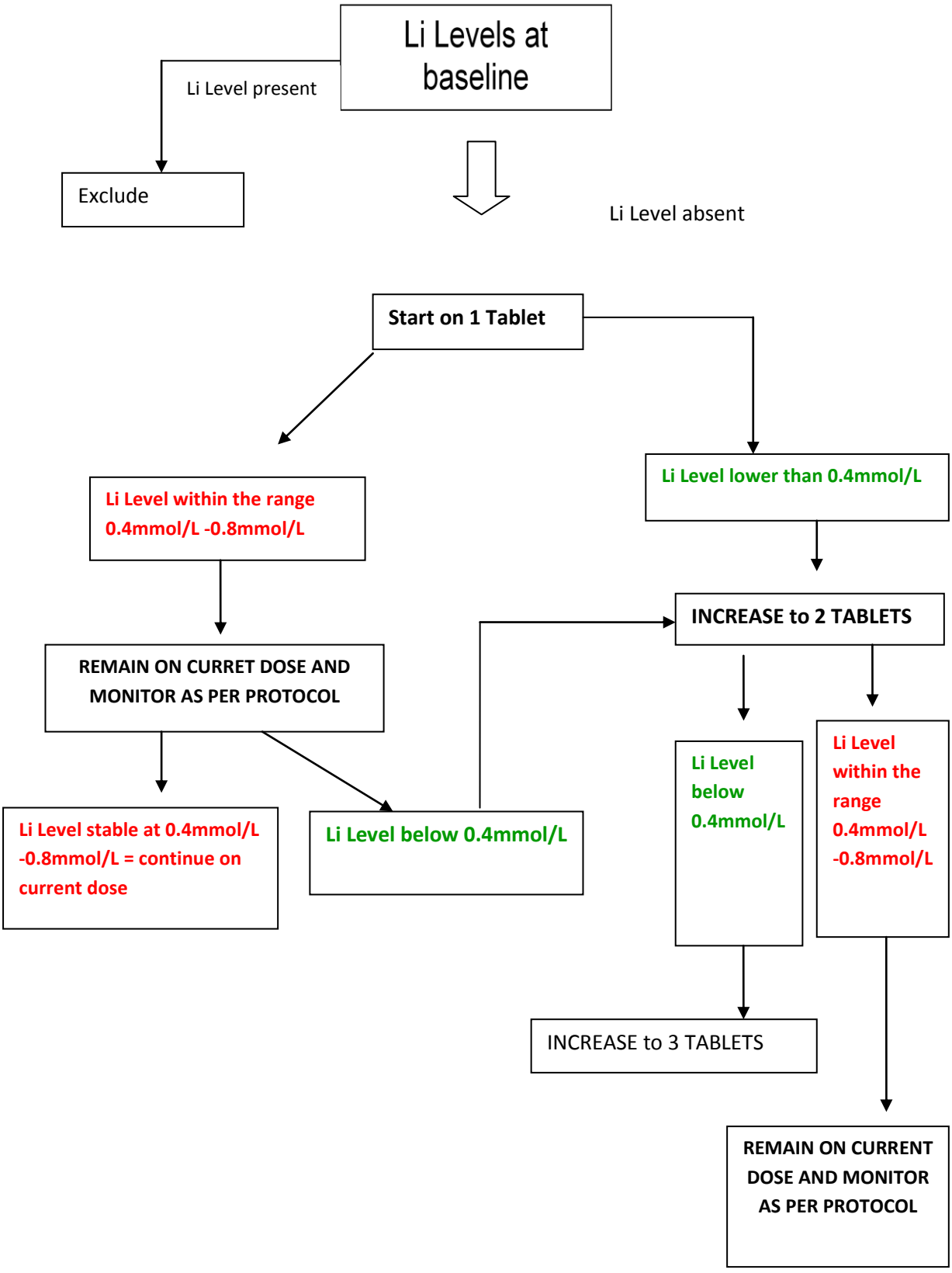
11. 3 Dose Schedule

Tablets were taken by participants using their normal methods for medicines management in a single dose at night. Participants were provided with written information from the doctor detailing the dose to be taken**.**

11. 4 Dose Titration

The following dose titration process was adhered to:

FLOW DIAGRAM 1: DOSE TITRATION PROCESS



11.5 Mode of Administration

Following stabilisation of blood levels over the first 3 months, plasma level monitoring can be measured every 3 months, except in the following circumstances, when monitoring needs to be done more frequently — presence of intercurrent illness, symptoms or signs of lithium toxicity, or if the patient is taking interacting drugs e.g. non-steroidal anti-inflammatory agents, diuretics, steroids, metronidazole, tetracycline, angiotensin converting enzyme (ACE) inhibitors; or if there is a change in fluid or sodium intake. If the study medication is given crushed via a feeding tube, as opposed to as whole tablets, monitoring of Li Levels will also need to be more frequent. All medication will be monitored by a lithium physician (unblinded).

11.6 Duration of treatment

Participants were scheduled to receive 105 tablets for (month 1, 2, and 3) 294 tablets at (months 6, 9, 12, and 15). Dose adjustment decisions meant that participants sometimes had surplus medication and were therefore asked at the end of each visit (months 1, 2, 3, 6, 9, 12,15, and 18) to return any surplus study drug in the original packaging to the research team, who verified and documented compliance and discussed any discrepancies immediately with the participant. All unused study medication and packaging was then sent to the local pharmacy where the study monitor checked and arranged collection of returns. Monitoring checks were carried out between the eCRF and pharmacy to ensure the number of tablets returned is correctly documented.

12.0 Criteria for Evaluation

12.1 Safety

The aim of the analysis is to estimate the difference in the rate of adverse events experienced by the two treatment groups.

12.1.1 Serious adverse events

Serious adverse events (SAEs) will be determine by:

- 95% confidence interval for the hazard ratio (risk of a serious adverse event for) a patient randomised to LiCO3 compared with a patient randomised to placebo
    a. For all serious adverse events
    b. For all serious adverse events excluding death

    (SPSS/stata)

- 95% confidence interval for the hazard ratio of having at least one susar (a patient randomised to LiCO3 compared with a patient randomised to placebo). (SPSS/stata)

12.1.2 Non serious adverse events

Non serious adverse events (non-SAEs) will be reported by body system. A 95% confidence interval for the incidence rate ratio will be based on a negative binomial regression with days alive in study included as an exposure variable. (stata)

12.1.3 Missing data

Quality of life scores will be calculated in accordance with their author's instructions. In the absence of any rule for missing data data imputation will be used provided at least half the items in any scale have been completed (imputed missing value = mean value of non missing items)

Missing survival date is dealt with by using the date of censoring and the status of the patient at that point.

The secondary outcomes are being analysed using mixed models that make use of all data available. The analysis is adjusted to take into account that some subjects have provided more information than others.

If there is a difference in survival rates we will have more "missing" outcome data in one group than another. If this situation occurs the data will be analysed using joint modelling as described above. Thus estimates of functional health status and quality of life will be adjusted for differences in survival rates.

There will be no other data imputation.

12.1.4 Sub group analyses

No subgroup analysis is planned.

12.2 Efficacy

12.2.1 Primary analysis:

The primary outcome was survival at 18 months. Survival rates at 18 months in the two arms (Lithium treatment versus control) will be compared using Kaplan–Meier Test. Results were also to be given in the form of a 95% confidence interval for the relative risk of survival.

12.2.2 Secondary analysis:

Secondary outcomes including the ALSFRS-R was to be assessed at baseline, 3, 6, 9, 12, 15, and 18 months. The main statistical challenge in analysing such data is to take into account incomplete data which may be due to a number of factors most notably of which will be the death of individual patients; in this study we anticipate that survival rates may differ by at least 20%. It is necessary to take into account the differing dropout rates and the non-randomness of the drop out when comparing functional status between the two groups. This was to be done by jointly modelling the survival data and repeated measurements data [35]. The survival data are analysed using a Cox proportion hazards model incorporating random effects. Functional outcomes are modelled using mixed models appropriate for repeated measures. A key feature of each of these models is that within each of them it is possible to fit a latent variable that can be conceptualised as the patient's propensity to experience poor outcomes (in the context of survival analysis this is usually referred to as frailty). It is the inclusion of this latent variable that allows us to adjust our estimates of the treatment effect to allow for the different rates of drop out in each group. Both models are estimated simultaneously; parameter estimates are based on maximising the joint likelihood over both the survival and repeated measures data. Within this framework it will estimate the effect of Lithium treatment on survival and functional status/quality of life allowing for key baseline covariates including site of onset of disease and possible differences between centres. These methods will be implemented using software that has been developed as part of an MRC funded programme of work (Grant G0400615; statistical methodology for longitudinal studies in clinical research; Williamson PR, Diggle PJ and Henderson R, unpublished work).

13.0 Statistical Method

The sample size will be based on detecting a difference in survival rates at 18 months using Fleiss' method for a proportion incorporating a continuity correction. Two groups of 110 subjects will give us 80% power to detect a difference of 17.5% in survival rates (65% versus 82.5%) assuming a type

1 error rate of 5%.

Sensitivity analyses will include per-protocol and per-treatment analyses, as specified in the statistical plan to be developed by the TSC and the DMEC and approved by NRES and local Ethics committees, prior to un-blinding.

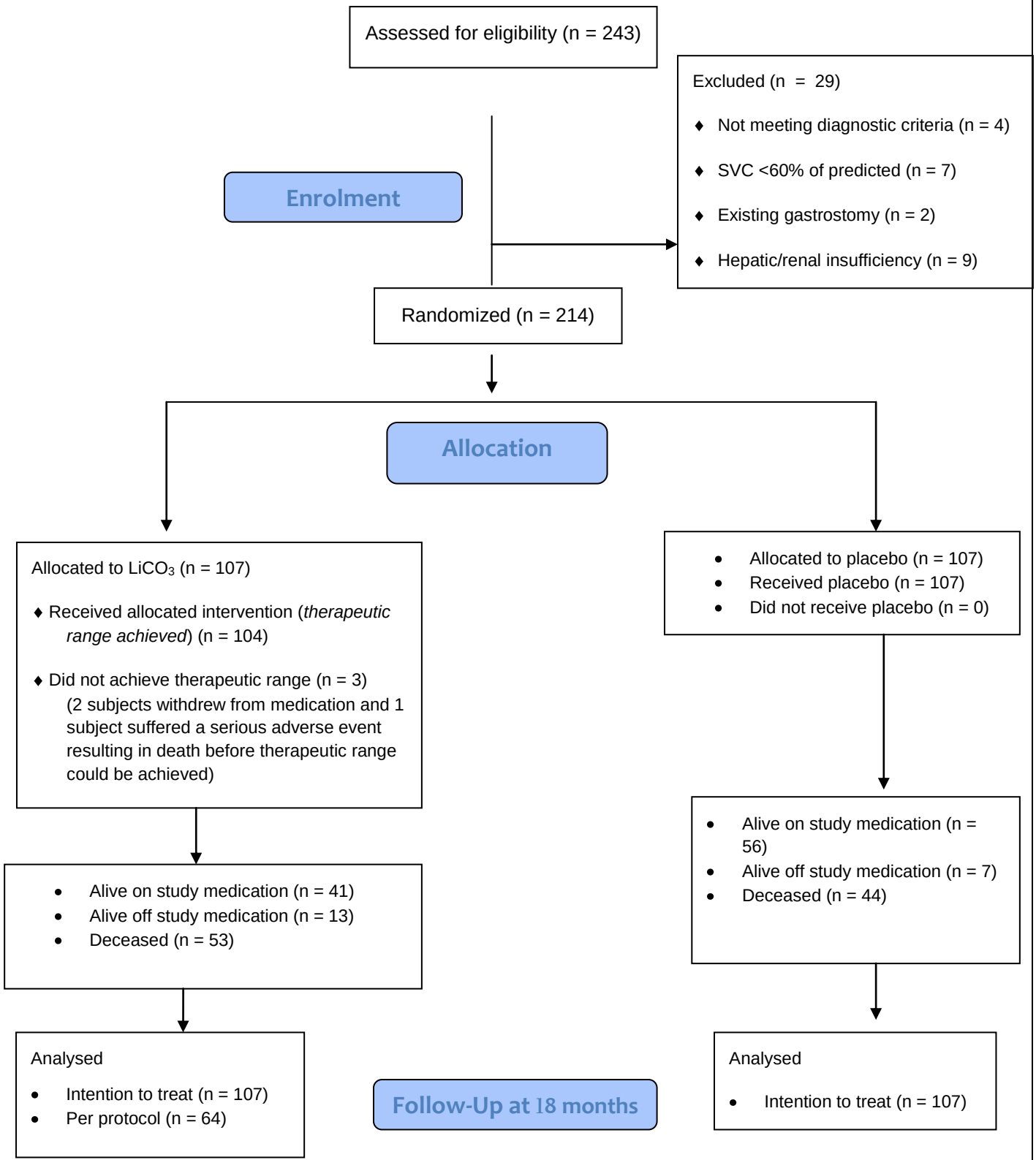
No interim analysis is planned although there will be pre-defined stopping criteria agreed by the Trial Steering Committee (TSC) and the Independent Data Monitoring and Ethics Committee (DMEC).

The population used in the efficacy analyses is the Intention To Treat (ITT) population. This population will consist of all patients randomised to treatment, who took at least one dose of double-blind treatment, regardless of compliance with the study protocol and procedures. If the primary analysis event (i.e., death) does not occur, a patient's data will be considered censored either on his/her planned study end date, or on the cut-off date for the study as a whole, or when the patient becomes lost to follow-up, whichever is the earlier. Data will be included in the analysis regardless of whether the patient is still receiving double-blind study treatment or complying with the prescribed regimen. The Trial Steering Committee and/or Data Monitoring Committee may decide that sensitivity analyses (endpoints and population to be defined) are also required. The population used to assess safety and tolerability will consist of all patients randomised to treatment that took at least one dose of double-blind treatment and provided at least some data thereafter, regardless of compliance with the study protocol and procedures. Descriptive statistics of baseline data and summaries of safety and tolerance data will be further subdivided by randomisation stratum (site of onset of the disease, Centre).

Demographics and population characteristics: Deviations from the protocol, with regard to both the entry criteria and the scheduled assessments and examinations, will be summarized. Individual deviations will be detailed and (if appropriate) commented upon. Treatment assignment by stratum and study site, and the numbers of measurements available for each parameter will be presented. Demographics, medical history, history of the disease, scores at baseline on all variables and scales assessed, and medication and other treatment received on entry will be summarized with tabular presentation of baseline comparability.

14.0 Results

FLOW DIAGRAM 2: LICALS CONSORT



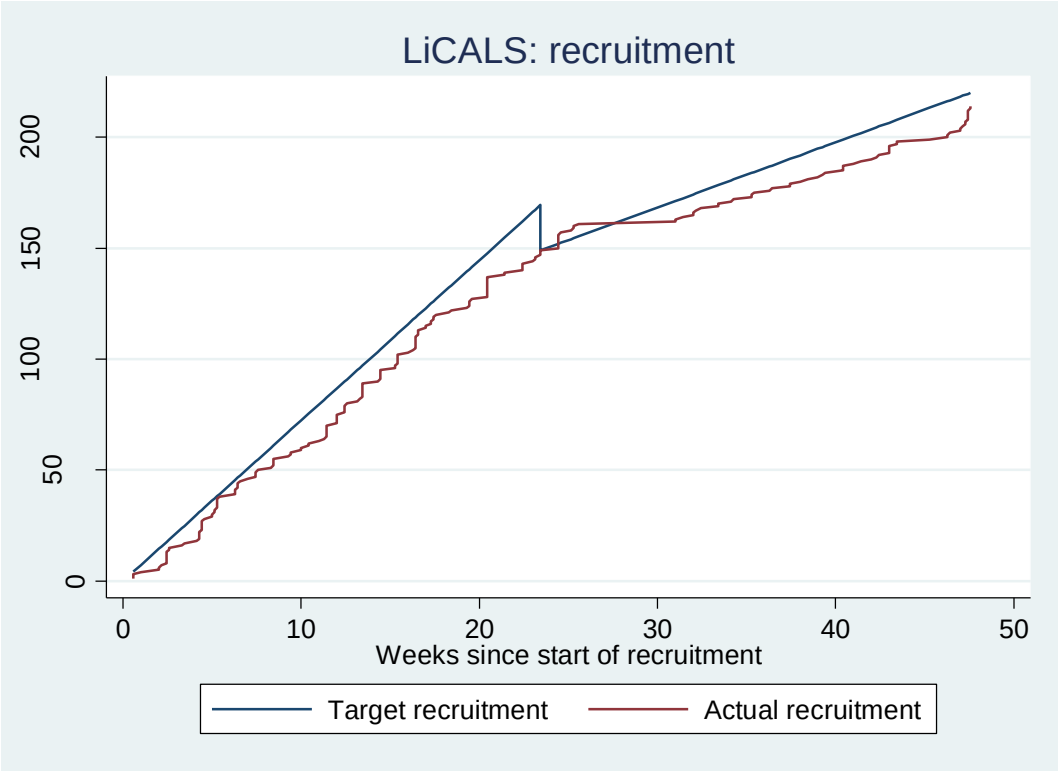
14.1 Recruitment

Number of participants anticipated to enter the study	220 were expected to recruited be over a 6 month period. Recruitment was initially scheduled to end 30 November 2009 unfortunately only 160 participants had been recruited at this time. Protocol amendment 03, dated 9 November 2009 permitted the extension of the recruitment to end April 2010. See graph 1
Number of participants Screened for the study	243 participants screened for eligibility.
Number of participants who were fully eligible and entered into the study:	214
Number of participants not fully eligible:	29

TABLE 3: RECRUITMENT BY CENTRE BY GROUP TO WHICH RANDOMISED

	Treatment allocation		
Centre	**Control**	**$LiCO_3$**	**Total**
Birmingham	14	12	26
KCL	10	9	19
Liverpool	12	13	25
Manchester	11	11	22
NHNN	11	11	22
Newcastle	9	9	18
Oxford	13	12	25
Plymouth	9	10	19
Preston	7	9	16
Sheffield	11	11	22
	107	107	214

Graph 1: Graph of cumulative recruitment



The recruitment target was 220 patients. Recruitment started on 1st June 2009 with a scheduled end at 31st December 2009. In November 2009 the recruitment period was extended until 30th April 2010 at which point a total of 214 patients had been randomised.

14. 1.1 Baseline Characteristics & Treatment Allocation

14.1.1.1 Gender

TABLE 4: RECRUITMENT BY GENDER AND TRIAL ARM

		Treatment allocation		
		Control	$LiCO_3$	Total
Gender	Female	30 (28.0%)	36 (33.6%)	66 (30.8%)
	Male	77 (72.0%)	71 (66.4%)	148 (69.2%)
Total		107	107	214

Approximately 30% of the sample was female.

TABLE 5: RECRUITMENT BY SITE BY GENDER

		Gender		
		Female	Male	Total
Site	Birmingham	8 (30.7%)	18	26
	KCL	3 (15.8%)	16	19
	Liverpool	6 (24.0%)	19	25
	Manchester	4 (18.2%)	18	22
	NHNN	7 (31.8%)	15	22
	Newcastle	8 (44.4%)	10	18
	Oxford	8 (32.0%)	17	25
	Plymouth	7 (36.8%)	12	19
	Preston	8 (50.0%)	8	16
	Sheffield	7 (31.8%)	15	22
Total		66 (30.8%)	148	214

14.1.1.2 Age

The mean age of the sample was just under 60.

TABLE 6: AGE BY TREATMENT ALLOCATION

Treatment allocation	Mean	N	Std. Deviation
Control	59.5	107	11.5
$LiCO_3$	59.7	107	9.9
Total	59.6	214	10.7

14.1.1.3 Ethnicity

Two hundred and ten patients were categorised as “white”, three patients were categorised as “black” and one patient was categorised as “other”.

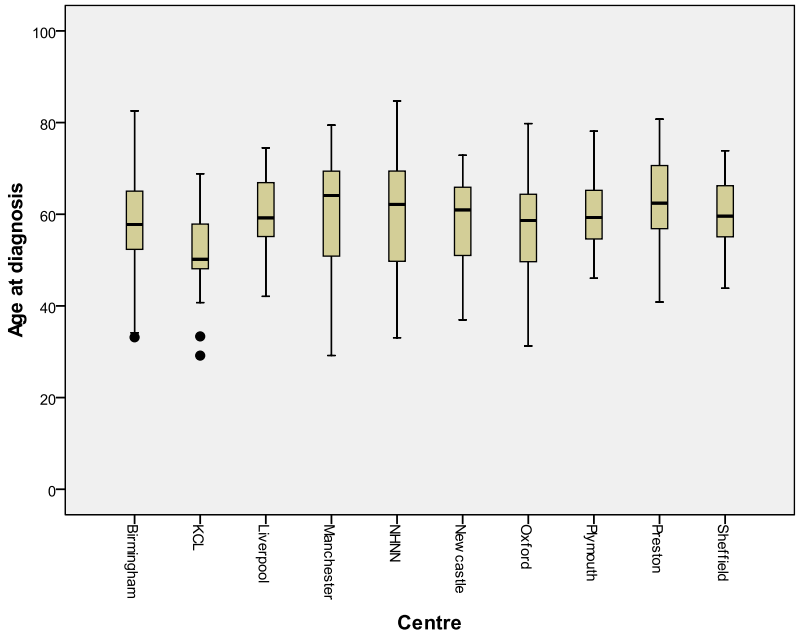
14.1.1.4 ALS history

Age at diagnosis ranged from 29 to 85 with a mean of 59 years. The two groups were well balanced:

TABLE 7: AGE IN YEARS AT DIAGNOSIS BY TREATMENT GROUP

Treatment allocation	Mean	N	Std. Deviation
Control	58.9	107	11.6
$LiCO_3$	59.1	107	10.0
Total	59.0	214	10.8

BOX PLOT 1: AGE AT DIAGNOSIS BY CENTRE



Time in weeks from onset of symptoms to diagnosis and time in weeks from diagnosis to recruitment

Time from onset symptoms to diagnosis ranged from 4 weeks to 138 weeks; time from diagnosis of ALS to recruitment ranged from 4 weeks to 131 weeks.

TABLE 8: TIME IN WEEKS FROM ONSET OF SYMPTOMS TO DIAGNOSIS AND TIME IN WEEKS FROM DIAGNOSIS TO RECRUITMENT: DESCRIPTIVE STATISTICS

	N	Minimum	Maximum	Mean	Std. Deviation
Time in weeks from onset of symptoms to diagnosis of ALS	214	4.4	138.4	46.668	27.0166
Time in weeks from diagnosis of ALS to recruitment	214	4.4	130.7	35.405	28.5317

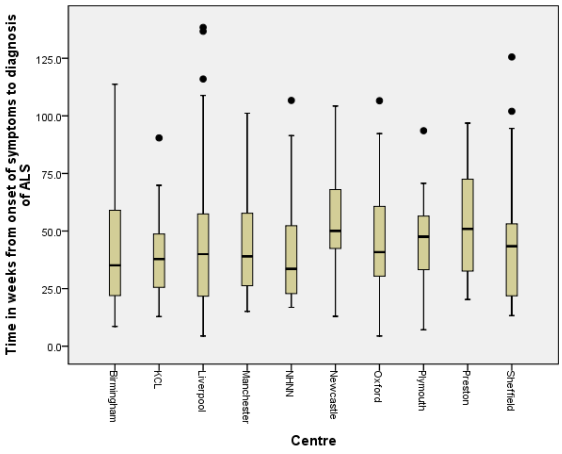
TABLE 9: TIME IN WEEKS FROM ONSET OF SYMPTOMS TO DIAGNOSIS AND TIME IN WEEKS FROM DIAGNOSIS TO RECRUITMENT BY TREATMENT GROUP: GROUP MEANS

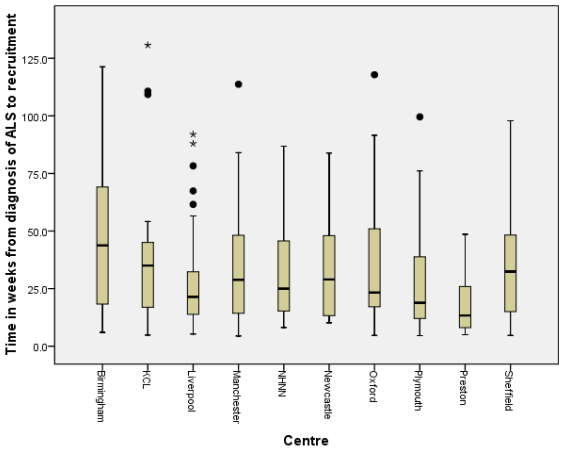
Treatment allocation		Time in weeks from onset of symptoms to diagnosis of ALS	Time in weeks from diagnosis of ALS to recruitment
Control	Mean	47.0	36.8
	N	107	107
	Std. Deviation	27.8	29.0
$LiCO_3$	Mean	46.3	34.0
	N	107	107
	Std. Deviation	26.3	28. 1

TABLE 10: TIME IN WEEKS FROM ONSET OF SYMPTOMS TO DIAGNOSIS AND TIME IN WEEKS FROM DIAGNOSIS TO RECRUITMENT BY CENTRE

Centre		Time in weeks from onset of symptoms to diagnosis of ALS	Time in weeks from diagnosis of ALS to recruitment
Birmingham	Mean	44.060	49.731
	N	26	26
	Std. Deviation	29.3840	36.6751
KCL	Mean	40.444	42.376
	N	19	19
	Std. Deviation	19.7930	35.8858
Liverpool	Mean	50.497	31.326
	N	25	25
	Std. Deviation	40.2038	26.3073
Manchester	Mean	41.786	37.422
	N	22	22
	Std. Deviation	22.3159	29.0219
NHNN	Mean	41.078	34.058
	N	22	22
	Std. Deviation	23.5917	24.8137
Newcastle	Mean	56.659	32.524
	N	18	18
	Std. Deviation	25.4419	21.9965
Oxford	Mean	47.206	34.326
	N	25	25
	Std. Deviation	25.1275	28.0998
Plymouth	Mean	46.835	29.865
	N	19	19
	Std. Deviation	21.1978	25.8992
Preston	Mean	53.143	18.045
	N	16	16
	Std. Deviation	24.6941	13.0863
Sheffield	Mean	47.604	37.416
	N	22	22
	Std. Deviation	28.8794	26.7829
Total	Mean	46.668	35.405
	N	214	214
	Std. Deviation	27.0166	28.5317

BOX PLOTS 2 &3 : TIME IN WEEKS FROM ONSET OF SYMPTOMS TO DIAGNOSIS AND FROM DIAGNOSIS TO RECRUITMENT BY CENTRE





14.1.1.5 Type of Onset

TABLE 11: TYPE OF ONSET BY TREATMENT GROUP

		Type of onset		
		0. Sporadic	1. Familial	Total
Treatment allocation	Control	106 (99.1%)	1	107
	$LiCO_3$	103 (96.3%)	4	107
Total		209 (97.7%)	5	214

14.1.1.6 Site of Onset

TABLE 12: SITE OF ONSET BY TREATMENT GROUP

		Site of onset		
		0. Limb	1. Bulbar	Total
Treatment allocation	Control	83 (77.6%)	24	107

	$LiCO_3$	84 (78.5%)	23	107
Total		167 (78.0%)	47	214

14.1.1.7 Handedness

TABLE 13: HANDEDNESS BY TREATMENT GROUP

		Handedness			
		1. Right	2. Left	3. Ambidextrous	Total
Treatment allocation	Control	94 (87.8%)	11	2	107
	$LiCO_3$	92 (86.0%)	15	0	107
Total		186 (86.9%)	26	2	214

14.1.1.8 Diagnosis by El Escorial Criteria

TABLE 14: DIAGNOSIS BY EL ESCORIAL CRITERIA BY TREATMENT GROUP

		Treatment allocation		
		Control	LiCO3	Total
El Escorial criteria	Clinically definite ALS	41	41	82
	Clinically probable ALS	43	37	80
	Clinically probable - laboratory supported ALS	18	20	38
	Clinically possible ALS	5	9	14

14.1.1.9 ECG

Date of ECG was recorded for all 214 patients.

TABLE 15 &16: ABNORMALITIES BY GROUP TO WHICH RANDOMISED

		Are there any abnormalities with ECG?			
		Not recorded	No	Yes	Total
Treatment allocation	Control	1	73	33	107
	$LiCO_3$	0	73	34	107
Total		1	146	67	214

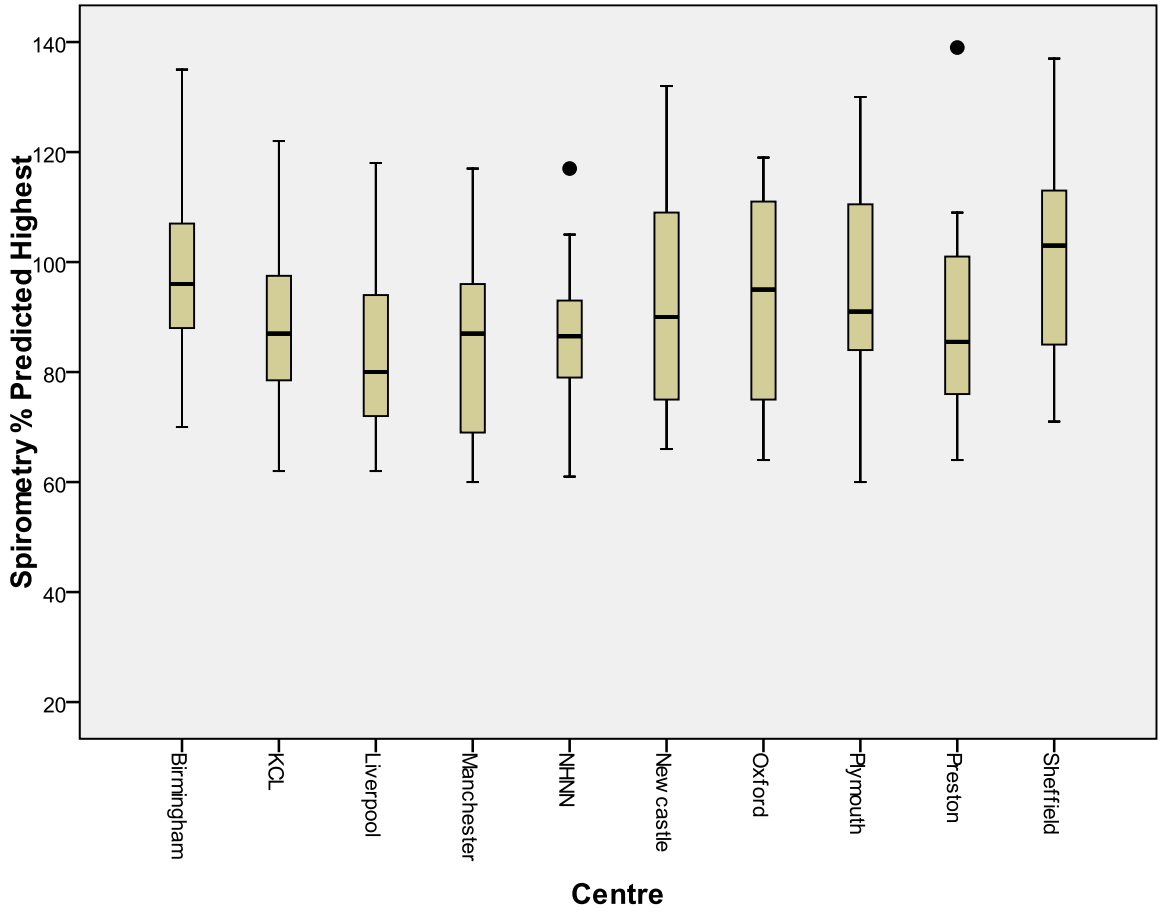
The ECG result was missing for one patient. For the 67 patients with an abnormal result the abnormality was classified as clinically significant in 8 cases:

		Are ECG abnormalities clinically significant?		
		No	Yes	Total
Treatment allocation	Control	28	5	33
	$LiCO_3$	31	3	34
Total		59	8	67

But the clinically significant abnormalities did not prevent entry into the study

14.1.1.10 Spirometry

BOX PLOT4: SPIROMETRY VALUES BY CENTRE



BOX PLAT 5: SPIROMETRY VALUES BY GROUP TO WHICH RANDOMISED

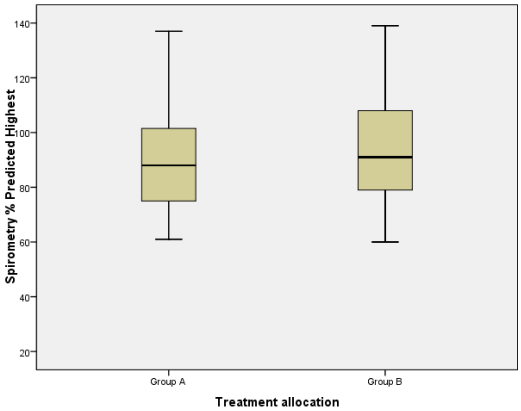


TABLE 17: SPIROMETRY % PREDICTED HIGHEST

Report

Spirometry % Predicted Highest

Treatment allocation	Mean	N	Std. Deviation
Group A	89.31	107	16.968
Group B	93.29	107	18.467
Total	91.30	214	17.804

14.1.1.11 Riluzole

TABLE 18: THREE PATIENTS HAD TWO COURSES OF RILUZOLE PRIOR TO RANDOMISATION:

Patient	Date randomised	1st course		2nd course	
		Started	Days before randomisation	Started	Days before randomisation
4009	02/09/2009	23/11/2008	283	06/07/2009	58
8002	02/07/2009	25/02/2009	127	04/06/2009	28
8022	29/03/2010	22/01/2010	66	27/02/2010	30

For these patients the last course is used to determine time on riluzole prior to entry to the study.

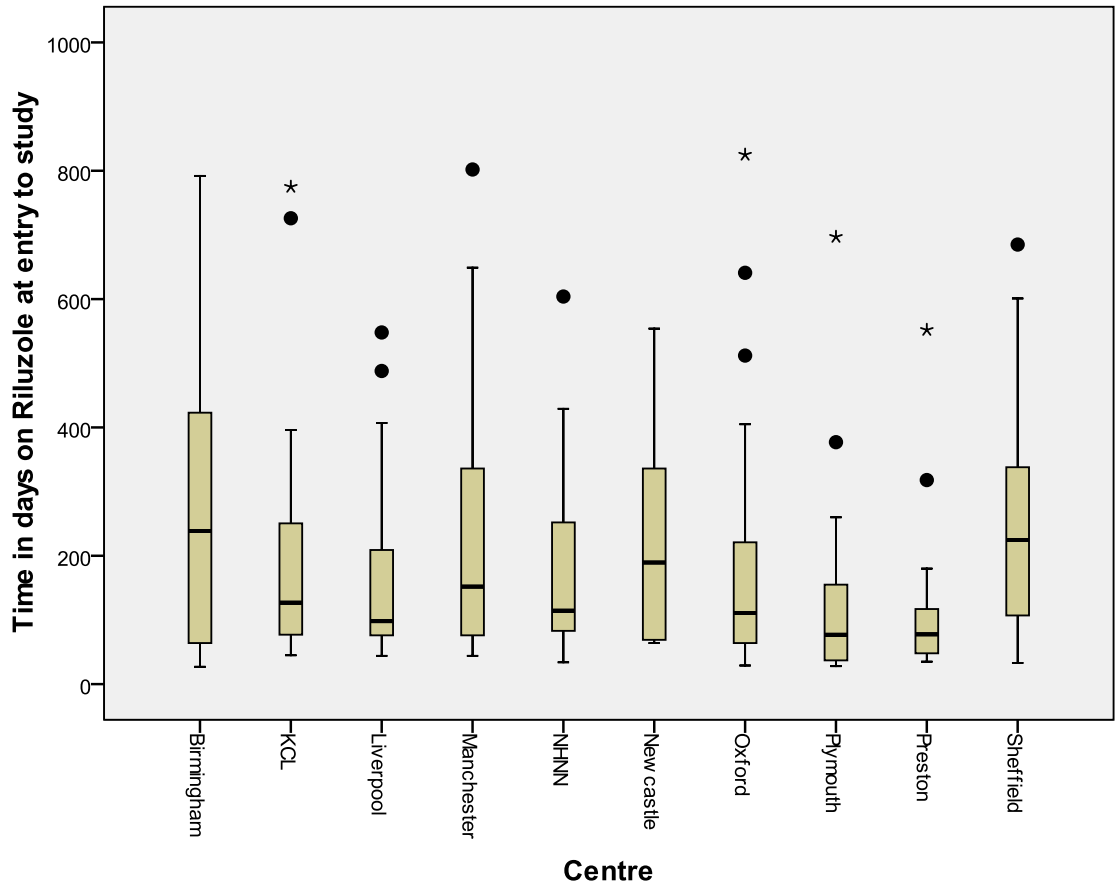
TABLE 19: DESCRIPTIVE RILUZOLE STATISTICS

	N	Minimum	Maximum	Mean	Std. Deviation
Time in days on Riluzole at entry to study	214	27	825	204.04	184.672

TABLE 20: TIME IN DAYS ON RILUZOLE AT ENTRY TO STUDY BY STUDY GROUP

Control	N	Valid	107
		Missing	0
	Median		121.00
	Minimum		27
	Maximum		792
$LiCO_3$	N	Valid	107
		Missing	0
	Median		118.00
	Minimum		28
	Maximum		825

BOX PLOT 6: TIME IN DAYS ON RILUZOLE AT ENTRY TO STUDY BY STUDY CENTRE



14.1.1.12 Vital signs

TABLE 21: VITAL SIGNS BY TREATMENT ARM

Treatment allocation		Temperature (°C)	Pulse rate (bpm)	Systolic BP	Diastolic BP
Control	Mean	36.484	74.39	135.02	84.07
	N	103	97	97	97
	Std. Deviation	.4311	12.156	16.932	12.012
LiCO3	Mean	36.403	76.69	132.63	83.62
	N	104	94	93	92
	Std. Deviation	.5113	13.899	15.802	15.290
Total	Mean	36.443	75.52	133.85	83.85
	N	207	191	190	189
	Std. Deviation	.4737	13.059	16.389	13.671

14.1.1.13 Health status at baseline

TABLE 22: HEALTH STATUS AT BASELINE

Variable		$LiCO_3$ (n = 107)	Control (n =107)
HADS			
Anxiety	(mean, sd)	4.59 (3.37)	4.46 (3.76)
Depression	(mean, sd)	3.89 (2.84)	4.00 (3.10)
ALSFRS-R	(mean, sd)	38.20 (5.66)	38.64 (5.72)
EQ-5D health state tariff	(mean, sd)	0.59 (0.30)	0.59 (0.28)
EQol health evaluation	(mean, sd)	68.50 (18.50)	70.07 (19.48)

The groups appear to be well balanced at baseline.

14.1. 2 Flow of patients through the study

TABLE 23: STATUS OF PATIENTS BY VISIT

Visit	Alive on study medication	Alive off study medication	Deceased
Week 1	212	2	0
Week 2	210	3	1
Week 3	206	7	1
Week 4	208	4	2
Week 8	204	8	2
Week 12	195	13	6
Month 6	168	27	19
Month 9	152	32	31
Month 12	127	35	52
Month 15	109	27	78
Month 18	97	20	97

14.1.3 Compliance with medication

The number of tablets prescribed to each patient was recorded in the medication log. The number of tablets returned to the pharmacy was recorded at visits at 4 weeks, 8 weeks, 12 weeks, 6 months, 9 months, 12 months and 18 months. By comparing the two sets of data it is possible to determine the proportion of tablets prescribed that were actually taken by the visit. A patient was deemed to be a complier provided that they took at least 75% of the tablets prescribed in each quarter. In applying this rule only visits at which the patient was alive were included (the exception being that the returns at four week were used to assess compliance for the two patients who died prior to the visit at four weeks).

TABLE 24: TREATMENT ALLOCATION

			Treatment allocation		
			Control	LiCO3	Total
Complier?	No	Count	31	43	74
		% within Treatment allocation	29.0%	40.2%	34.6%
	Yes	Count	76	64	140
		% within Treatment allocation	71.0%	59.8%	65.4%
Total		Count	107	107	214

One hundred and forty patients (65.4%) have been classed as compliers. Relative risk of being a complier ($LiCO_3$/placebo) = 0.84 (95% CI: 0.69, 1.03).

15.0 Safety Results

15.1 Non serious adverse events results

One thousand three hundred and sixty nine non serious adverse events were recorded. At least one non serious adverse event was recorded for 207 of the 214 study participants including 103 out of 107 patients in the control arm and 104 out of 107 patients in the patients randomised to receive $LiCO_3$. The mean number of events per patient in the control arm was 6.29; the mean number of events in the $LiCO_3$arm was 6.50.

Comparing the incidence of non-serious adverse events in the two groups using negative binomial regression [model adjusted for centre (variable = siteno), site of onset (variable = bulbar) and length of time in follow up (variable = stdydays)]:

STATA OUTPUT 1: NEGATIVE BINOMIAL REGRESSION MODEL

```
Random-effects negative binomial regression     Number of obs      =       214
Group variable (i): siteno                      Number of groups   =        10

Random effects u_i ~ Beta                       Obs per group: min =        16
avg =      21.4                                                    
                                                              max =        26

                                                Wald chi2(2)       =      2.69
Log likelihood  =  -592.5211                    Prob> chi2         =    0.2602

------------------------------------------------------------------------------
nevents |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
      bulbar |   1.088842   .1123146     0.83   0.409     .8895348    1.332805
       LiCO3 |   1.125746   .0935538     1.43   0.154     .9565377    1.324886
stdydays | (exposure)
------------+-----------------------------------------------------------------
       /ln_r |   3.744107    .655285                      2.459772    5.028442
       /ln_s |   4.119478   .6761617                      2.794225     5.44473
------------+-----------------------------------------------------------------
```

```
           r |   42.27126   27.69972                      11.70215     152.695
           s |    61.5271   41.60227                      16.34996    231.5348
-------------------------------------------------------------------------------
Likelihood-ratio test vs. pooled: chibar2(01) =     8.97 Prob>=chibar2 = 0.001
```

The incidence rate ratio ($LiCO_3$/control) = 1.13 (95% CI: 0.96, 1.32); the rate of reporting of events does not differ significantly between groups (p = .15).

TABLE 25: NON SERIOUS ADVERSE EVENTS BY BODY SYSTEM BY STUDY CENTRE

	Site										
Body system	Birm-ingham	KCL	Liver-pool	Man-chester	NHNN	New-castle	Oxford	Plym-outh	Pres-ton	Shef-field	Total
Allergies	1	0	0	0	3	0	2	0	0	0	6
Cardiovascular	8	11	2	4	4	3	18	10	5	13	78
Dermatological	16	8	7	12	3	0	25	9	7	3	90
Endocrine	6	2	0	6	3	1	4	5	0	3	30
Eyes, ear, nose, throat	21	4	12	11	2	2	11	4	2	6	75
Gastro-intestinal	43	34	29	29	10	15	36	24	30	25	275
Genito-urinary	11	8	6	1	4	3	4	10	4	10	61
Haematological	0	0	2	4	1	1	13	21	4	0	46
Hepatic	1	0	0	3	0	0	3	14	0	2	23
Immunological	0	0	6	0	1	0	4	2	2	4	19
Musculo-skeletal	27	15	30	21	14	11	14	22	33	17	204
Neurological	36	13	24	21	36	29	31	32	13	18	253
Other	1	0	0	0	0	0	2	0	0	1	4
Psychological	6	9	8	3	9	3	5	7	3	7	60
Respiratory	33	7	15	12	3	13	13	23	15	11	145
Total	210	111	141	127	93	81	185	183	118	120	1369

TABLE 26: NON SERIOUS ADVERSE EVENTS BY BODY SYSTEM BY TREATMENT GROUP

Bodysystem		Treatment allocation		
		Control	$LiCO_3$	Total
Allergies	Count	3	3	6
	% within Treatment allocation	.4%	.4%	.4%
Cardiovascular	Count	37	41	78
	% within Treatment allocation	5.5%	5.9%	5.7%
Dermatological	Count	49	41	90
	% within Treatment allocation	7.3%	5.9%	6.6%
Endocrine	Count	19	11	30
	% within Treatment allocation	2.8%	1.6%	2.2%
Eyes, ear, nose, throat	Count	38	37	75
	% within Treatment allocation	5.6%	5.3%	5.5%
Gastro-intestinal	Count	130	145	275
	% within Treatment allocation	19.3%	20.8%	20.1%
Genito-urinary	Count	29	32	61
	% within Treatment allocation	4.3%	4.6%	4.5%
Haematological	Count	23	23	46
	% within Treatment allocation	3.4%	3.3%	3.4%
Hepatic	Count	14	9	23
	% within Treatment allocation	2.1%	1.3%	1.7%
Immunological	Count	6	13	19
	% within Treatment allocation	.9%	1.9%	1.4%
Musculo-skeletal	Count	102	102	204
	% within Treatment allocation	15.2%	14.7%	14.9%
Neurological	Count	132	121	253
	% within Treatment allocation	19.6%	17.4%	18.5%
Other	Count	2	2	4
	% within Treatment allocation	.3%	.3%	.3%
Psychological	Count	23	37	60
	% within Treatment allocation	3.4%	5.3%	4.4%
Respiratory	Count	66	79	145
	% within Treatment allocation	9.8%	11.4%	10.6%
Total	Count	673	696	1369
	% within Treatment allocation	100.0%	100.0%	100.0%

TABLE 27: RELATED TO STUDY DRUG BY TRIAL ARM

		Related to Study Drug?					
		Definite	Probable	Possible	Remote	None	Total
Treatment allocation	Control	1	13	114	182	363	673
	$LiCO_3$	2	29	140	164	361	696
Total		3	42	254	346	724	1369

TABLE 28: SEVERITY BY TRIAL ARM

			Treatment allocation		
			Control	$LiCO_3$	Total
Severity	1. Mild	Count	423	412	835
		% within Treatment allocation	62.9%	59.2%	61.0%
	2. Moderate	Count	202	239	441
		% within Treatment allocation	30.0%	34.3%	32.2%
	3. Severe	Count	48	45	93
		% within Treatment allocation	7.1%	6.5%	6.8%
Total		Count	673	696	1369
		% within Treatment allocation	100.0%	100.0%	100.0%

15.2 Serious adverse events (including death)

One patient is recorded as having had a serious adverse event between two screening visits and prior to his/her signing the consent form. Since this event occurred before randomisation it has been excluded from the analysis.

At least one serious adverse event was recorded for 107 patients during the 18 month follow up period. Four patients had three recorded events; thirty patients had two recorded events and 83 patients had a single recorded adverse event.

TABLE 29A: SAEs BY TREATMENT ARM

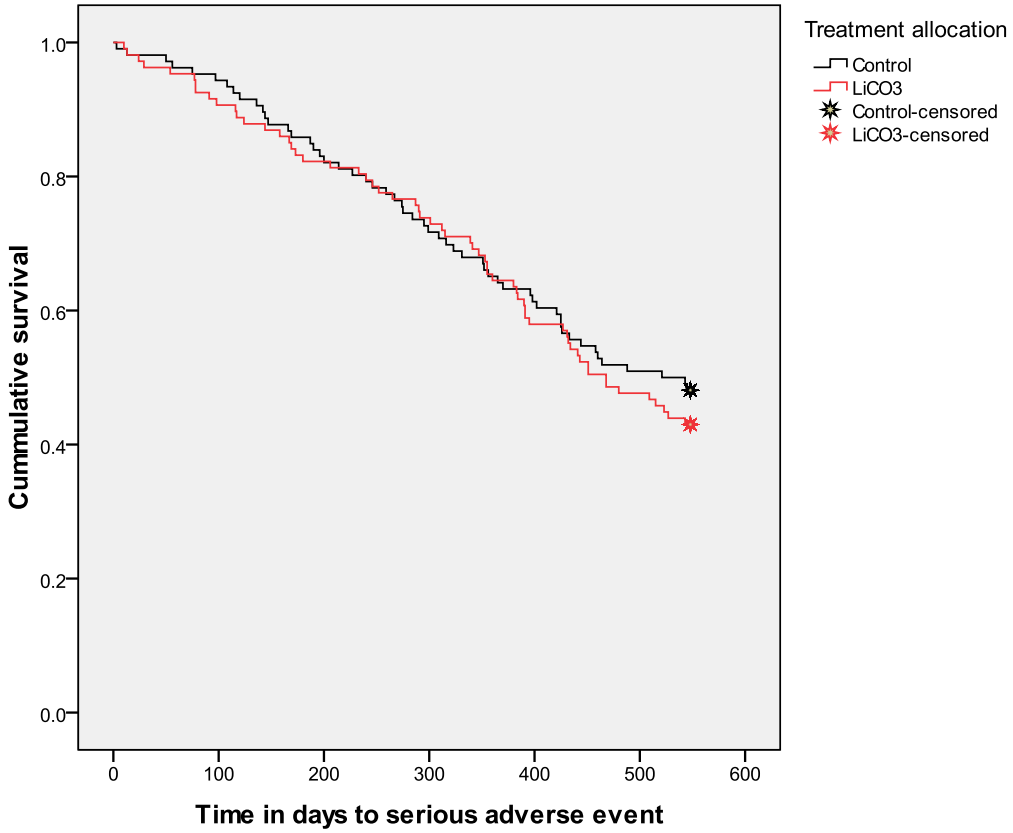
		Treatment allocation		
		Control	$LiCO_3$	Total
Number of entries in serious adverse events file	0	51	46	97
	1	41	42	83
	2	14	16	30
	3	1	3	4
Total		107	107	214

TABLE 29B: SAEs REPORTING

			Any SAE?		
			No	Yes	Total
Treatment allocation	Control	Count	51	56	107
		% within Treatment allocation	47.7%	52.3%	100.0%
	$LiCO_3$	Count	46	61	107
		% within Treatment allocation	43.0%	57.0%	100.0%
Total		Count	97	117	214
		% within Treatment allocation	45.3%	54.7%	100.0%

The relative risk of an SAE for patient randomised to $LiCO_3$ relative to that of a patient randomised to placebo is 1.09 with 95% CI: 0.58, 1.39. [There is no evidence that rate of adverse event reporting differs between the two groups].

TABLE 30: TIME TO FIRST SERIOUS ADVERSE EVENT



Pre specified analysis

- *95% confidence interval for the hazard ratio (risk of a serious adverse event for) a patient randomised to $LiCO_3$ compared with a patient randomised to placebo*
    a. *For all serious adverse events*
    b. *For all serious adverse events excluding death*

Fitting a Cox proportional hazards model the estimated hazard ratios are:

a. 95% confidence for hazard ratio ($LiCO_3$/control) = 0.79 to 1.65 (all events)
b. 95% confidence for hazard ratio ($LiCO_3$/control) = 0.52 to 1.36 (events excluding death)

Each of these confidence intervals includes 1 (corresponding to equal risk of adverse events). So the difference between groups is not statistically significant.

15.3 SUSARs

No suspected unexpected serious adverse reactions were reported.

15.4 Blood Lithium Levels

A "measurement" is a measurement of the concentration of Lithium in a blood sample. One hundred and seven patients were randomised to receive Lithium. For individual patients the number of measurements ranged from 1 to 21 with a mean of 10.7. The frequency distribution of these measurements is given in table 31

TABLE 31: FREQUENCY DISTRIBUTION OF NUMBER OF MEASUREMENTS OF LITHIUM CONCENTRATION

n	Frequency	Percent
1	1	.9
3	2	1.9
4	2	1.9
5	1	.9
6	4	3.7
7	7	6.5
8	11	10.3
9	12	11.2
10	8	7.5
11	7	6.5
12	19	17.8
13	20	18.7
14	4	3.7
15	2	1.9
16	3	2.8
17	1	.9
18	2	1.9
21	1	.9
Total	107	100.0

One hundred and four patients (97.2%) had at least one measurement in the therapeutic range (0.4 to 0.8 mmol/L). The mean number of measurements within the therapeutic range was 6.6.

The three patients who did not achieve therapeutic range were P02019; P06015 and P10008. One patient withdrew from medication after becoming pregnant; one patient withdrew from trial medication after an adverse event one week into the study; one patient had a serious adverse event leading to death before therapeutic range could be achieved.

TABLE 32A: NUMBER OF MEASUREMENTS WITHIN THERAPEUTIC RANGE

n	Frequency	Percent
0	3	2.8
1	3	2.8
2	5	4.7
3	8	7.5
4	4	3.7
5	11	10.3
6	12	11.2
7	16	15.0
8	14	13.1
9	12	11.2
10	13	12.1
11	4	3.7
12	1	.9
13	1	.9
Total	107	100.0

Considering the 104 patients for whom the therapeutic range was achieved the proportion of subsequent measurements that were within the therapeutic range varied from 15% to 100% with a mean of 82.1%.

Twenty five patients (23.4%) had at least one measurement above the recommended upper threshold of 0.8 mmol/L. Typically this was a single value that occurred while the appropriate dose for a patient was being ascertained.

TABLE 32B: NUMBER OF MEASUREMENTS ABOVE THRESHOLD OF 0.8 MMOL/L

n	Frequency	Percent
0	82	76.6
1	18	16.8
2	5	4.7
4	2	1.9
Total	107	100.0

15.5 ALS Interventions

15.5.1 Percutaneous endoscopic gastrostomy (PEG)

The date of gastrostomy was missing for one patient (P03005). It is assumed that it was during the 18 month follow up period.

Two patients (P04008 and P07012) had a gastrostomy prior to randomisation

Fifty nine patients had a gastrostomy during the follow up period.

One patient (P05014) had a gastrostomy after the end of the 18 month follow up period and is included in the following table as not having had a gastrostomy.

TABLE 33: PROPORTION OF PATIENTS HAVING A GASTROSTOMY BY TREATMENT ALLOCATION

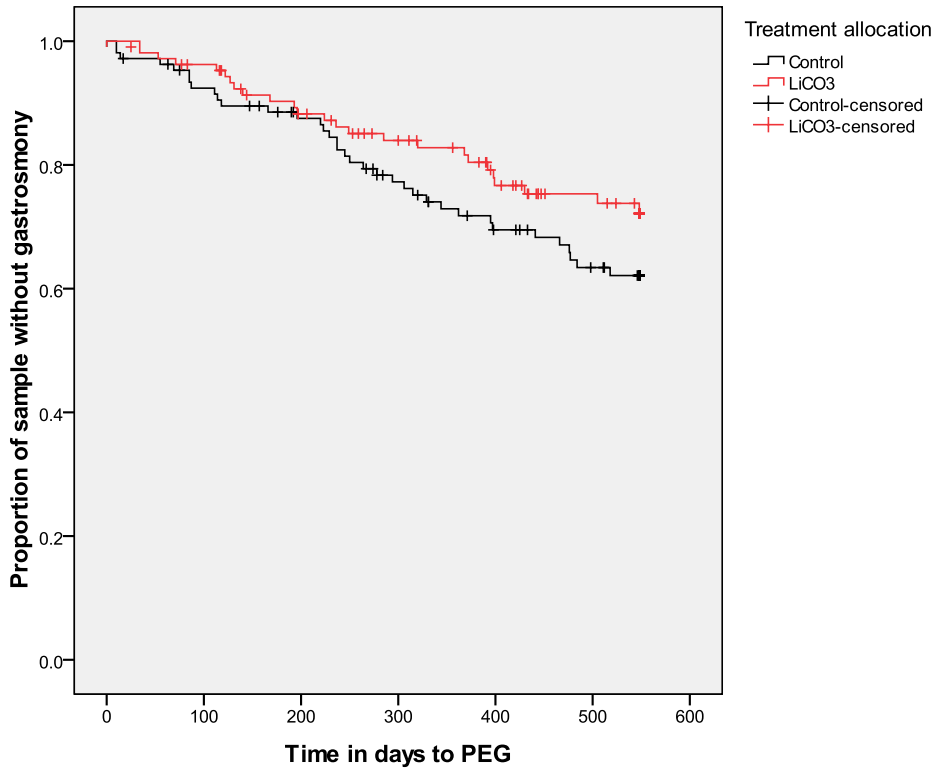
			Gastrostomy?		
			No	Yes	Total
Treatment allocation	Control	Count	71	36	107
		% within Treatment allocation	66.4%	33.6%	100.0%
	$LiCO_3$	Count	82	25	107
		% within Treatment allocation	76.6%	23.4%	100.0%
Total		Count	153	61	214
		% within Treatment allocation	71.5%	28.5%	100.0%

Relative risk of being having a gastrostomy ($LiCO_3$/placebo) = 0.69 (95% CI: 0.45, 1.07).

TABLE 34A: GASTROSTOMY BY STUDY CENTRE

			Gastrostomy?		
			No	Yes	Total
Centre	Birmingham	Count	14	12	26
		% within Centre	53.8%	46.2%	100.0%
	KCL	Count	16	3	19
		% within Centre	84.2%	15.8%	100.0%
	Liverpool	Count	18	7	25
		% within Centre	72.0%	28.0%	100.0%
	Manchester	Count	14	8	22
		% within Centre	63.6%	36.4%	100.0%
	NHNN	Count	18	4	22
		% within Centre	81.8%	18.2%	100.0%
	Newcastle	Count	17	1	18
		% within Centre	94.4%	5.6%	100.0%
	Oxford	Count	14	11	25
		% within Centre	56.0%	44.0%	100.0%
	Plymouth	Count	12	7	19
		% within Centre	63.2%	36.8%	100.0%
	Preston	Count	13	3	16
		% within Centre	81.3%	18.8%	100.0%
	Sheffield	Count	17	5	22
		% within Centre	77.3%	22.7%	100.0%
Total		Count	153	61	214
		% within Centre	71.5%	28.5%	100.0%

TABLE 34B: SURVIVAL PLOT: TIME TO GASTROSTOMY BY TREATMENT ALLOCATION



15.5.2 Non invasive ventilation

One patient (P01010) had non invasive ventilation after the end of the 18 month follow up period. Fifty six patients had non invasive ventilation during the follow up period.

TABLE 35: PROPORTION OF PATIENTS HAVING NON INVASIVE VENTILATION BY TREATMENT ALLOCATION

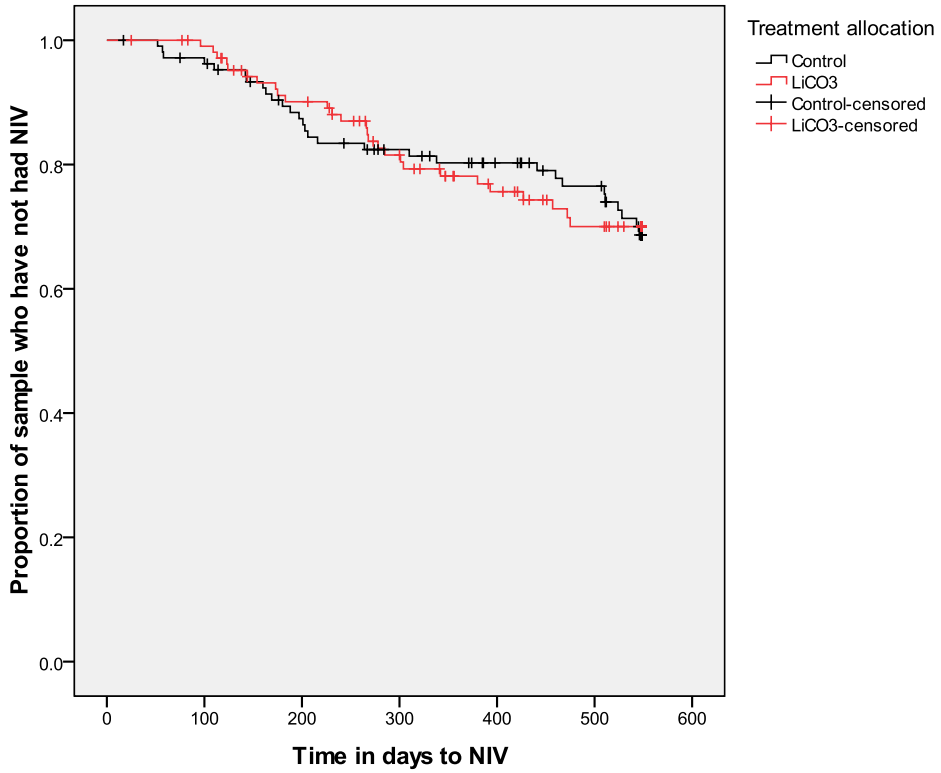
			NIV?		
			No	Yes	Total
Treatment allocation	Control	Count	78	29	107
		% within Treatment allocation	72.9%	27.1%	100.0%
	LiCO3	Count	80	27	107
		% within Treatment allocation	74.8%	25.2%	100.0%
Total		Count	158	56	214
		% within Treatment allocation	73.8%	26.2%	100.0%

Relative risk of being receiving non invasive ventilation ($LiCO_3$/placebo) = 0.93 (95% CI: 0.59, 1.46).

TABLE 36: NON INVASIVE VENTILATION BY STUDY CENTRE

			NIV?		
			No	Yes	Total
Centre	Birmingham	Count	15	11	26
		% within Centre	57.7%	42.3%	100.0%
	KCL	Count	18	1	19
		% within Centre	94.7%	5.3%	100.0%
	Liverpool	Count	19	6	25
		% within Centre	76.0%	24.0%	100.0%
	Manchester	Count	14	8	22
		% within Centre	63.6%	36.4%	100.0%
	NHNN	Count	19	3	22
		% within Centre	86.4%	13.6%	100.0%
	Newcastle	Count	14	4	18
		% within Centre	77.8%	22.2%	100.0%
	Oxford	Count	19	6	25
		% within Centre	76.0%	24.0%	100.0%
	Plymouth	Count	13	6	19
		% within Centre	68.4%	31.6%	100.0%
	Preston	Count	12	4	16
		% within Centre	75.0%	25.0%	100.0%
	Sheffield	Count	15	7	22
		% within Centre	68.2%	31.8%	100.0%
Total		Count	158	56	214
		% within Centre	73.8%	26.2%	100.0%

FIGURE 1: SURVIVAL PLOT TIME TO NON INVASIVE VENTILATION BY TREATMENT ALLOCATION



16.0 Primary Outcome:

16.1 Survival

Survival rate at 18 months

One hundred and seventeen patients were still alive 18 months post randomisation

TABLE 37: SURVIVAL AT MONTH 18 BY TREATMENT GROUP

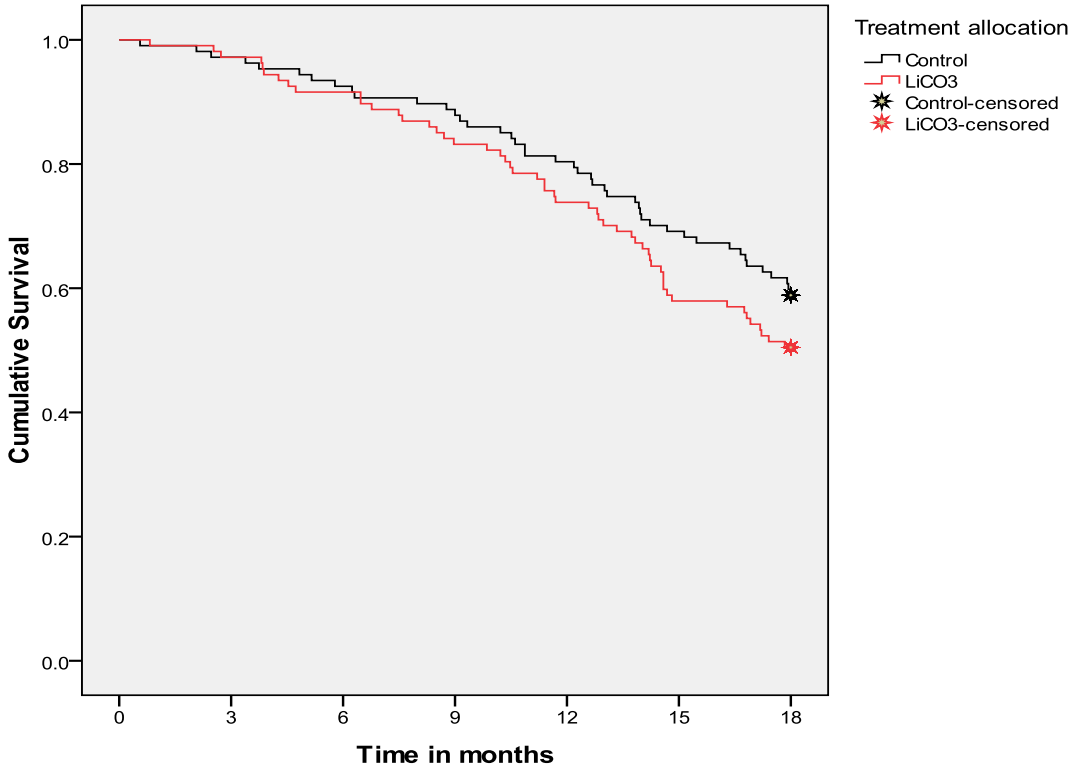
	Status at 18 months		
	Alive	Deceased	Total
Control	63 (58.9%)	44	107
$LiCO_3$	54 (50.5%)	53	107
Total	117 (54.7%)	97	214

Relative risk of survival at 18 months for patients on Lithium is 0.86 with 95% CI: 0.67, 1.10.

16.2 Time to death

Time to death ranged from 17 to 548 days with a mean of 338.3 days.

FIGURE 2: CUMULATIVE SURVIVAL BY TREATMENT GROUP



16.3 Primary endpoint

The primary analysis was defined as:

- *Survival rates at 18 months in the two arms (patients randomised to Lithium treatment versus patients randomised to placebo) will be compared using the log rank test. Two tailed test. Significance level set at 5%.*

Mantel-Cox Log rank chi-squared statistic:

The difference in survival functions is not statistically significant. We get a similar result when we adjust for differences between sites: Adjusted Mantel-Cox Log rank chi-squared statistic:

.

TABLE 38: SURVIVAL RATES AT 18 MONTHS BY STUDY CENTRE

	Group to which randomised					
	Control		$LiCO_3$		Total	
Centre	Baseline n	Alive (18m) n (%)	Baseline n	Alive (18m) n (%)	Baseline n	Alive (18m) n (%)
Birmingham	14	9 (64.3%)	12	11 (91.7%)	26	20 (76.9%)
KCL	10	8 (80.0%)	9	5 (55.6%)	19	13 (68.4%)
Liverpool	12	5 (41.7%)	13	6 (46.2%)	25	11 (44.0%)
Manchester	11	9 (81.8%)	11	10 (90.9%)	22	19 (86.4%)
NHNN	11	6 (54.5%)	11	2 (18.2%)	22	8 (36.4%)
Newcastle	9	5 (55.6%)	9	3 (33.3%)	18	8 (44.4%)
Oxford	13	8 (61.5%)	12	4 (33.3%)	25	12 (48.0%)
Plymouth	9	4 (44.4%)	10	3 (30.0%)	19	7 (36.8%)
Preston	7	4 (57.1%)	9	5 (55.6%)	16	9 (56.3%)
Sheffield	11	5 (45.5%)	11	5 (45.5%)	22	10 (45.5%)
Total	**107**	**63 (58.9%)**	**107**	**54 (50.5%)**	**214**	**117 (54.7%)**

TABLE 39: SURVIVAL RATES AT 18 MONTHS BY SITE OF ONSET

	Group to which randomised					
	Control		$LiCO_3$		Total	
Onset	Baseline n	Alive (18m) n (%)	Baseline n	Alive (18m) n (%)	Baseline n	Alive (18m) n (%)
Limb	84	52 (61.9%)	83	45 (54.2%)	167	97 (58.1%)
Bulbar	23	11 (47.8%)	24	9 (37.5%)	47	20 (42.6%)
Total	**107**	**63 (58.9%)**	**107**	**54 (50.5%)**	**214**	**117 (54.7%)**

We can adjust the log rank test for difference between site of onset.

- Adjusted Mantel-Cox Log rank chi-squared statistic: .

16.4 Secondary analysis of primary endpoint

- *Intention to treat analysis of survival rates at 18 months. Logistic regression analysis with adjustment for randomisation strata. Results will be given in the form of a 95% confidence interval for the relative odds of survival. (statistical package: stata)*

First fitting an unadjusted logistic regression model (dependent variable is survival at 18 months; explanatory variable is treatment allocation) we get the following result:

STATA OUTPUT 2: UNADJUSTED MODEL

```
Logistic regression                                     Number of obs   =        214
                                                        LR chi2(1)      =       1.53
                                                        Prob > chi2     =     0.2162
Log likelihood = -146.63293                             Pseudo R2       =     0.0052

------------------------------------------------------------------------------
        s18m | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       LiCO3 |   .7115903   .1961548    -1.23   0.217     .4145629    1.221433
------------------------------------------------------------------------------
```

Unadjusted odds ratio: 0.71 (95% CI: 0.41, 1.22).

Next including variation between centres as a random effect and fitting a difference in outcome between limb and bulbar site of onset:

Stata output 2 treatment affect adjusted for differences between centres and site of onset

```
Random-effects logistic regression              Number of obs      =       214
Group variable (i): siteno                      Number of groups   =        10

Random effects u_i ~ Gaussian                   Obs per group: min =        16
                                                               avg =      21.4
                                                               max =        26

                                                Wald chi2(2)       =      3.45
Log likelihood  = -142.56946                    Prob > chi2        =    0.1782

------------------------------------------------------------------------------
        s18m |         OR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      bulbar |   .6019148   .2146279    -1.42   0.155     .2992386    1.210744
       LiCO3 |   .7085354   .2032859    -1.20   0.230     .4037786    1.243311
-------------+----------------------------------------------------------------
    /lnsig2u |  -1.282547   .8276895                     -2.904789    .3396947
-------------+----------------------------------------------------------------
     sigma_u |   .5266214   .2179395                      .2340093    1.185124
         rho |   .0777445   .0593456                      .0163726    .2991911
------------------------------------------------------------------------------
Likelihood-ratio test of rho=0: chibar2(01) =     4.60 Prob >= chibar2 = 0.016
```

Adjusted odds ratio: 0.71 (95% 0.40, 1.24). There is almost no change in the odds ratio when we adjust for randomisation strata.

16.5 Per protocol analysis of primary endpoint

- *Per protocol analysis of time to death (censored at 18 months) using a Cox proportional hazards model. Patients will only be included in this analysis if they have taken at least 75% of tablets prescribed in any quarter (stata).*

Applying this definition of compliance:

TABLE 40: COMPLIANCE BY TREATMENT ARM

			Treatment allocation		
			Control	LiCO3	Total
Complier?	No	Count	31	43	74
		% within Treatment allocation	29.0%	40.2%	34.6%
	Yes	Count	76	64	140
		% within Treatment allocation	71.0%	59.8%	65.4%
Total		Count	107	107	214

One hundred and forty patients (65.4%) have been classed as compliers. Relative risk of being a complier ($LiCO_3$/placebo) = 0.84 (95% CI: 0.69, 1.03).

95% confidence interval for hazard ratio ($LiCO_3$/placebo) based o n Cox proportional hazards model is from 0.90 to 2.02 (p = 0.15). There is no evidence that treatment with $LiCO_3$ increased survival in this patient population.

17.0 Secondary outcomes

Three secondary outcomes were considered; the first outcome considered is functional status as measured by the ALS Functional Rating Scale-Revised scores. We sum the score on the 12 individual ALS questions resulting in an overall score between 0 and 48, 0 being the worst score and 48 the best score. For missing values we used as an imputed value the mean value of non-missing items if at least half the items in the ALSFRS-R questionnaire has been completed. Quality of life is measured by the EuroQol questionnaire. The scores on the first 5 questions are used to compute the EQ5-D health state tariff and the last question gives the EuroQol health evaluation. The EQ5-D health state tariff lies between 1 (best score) and -0.59 (worst score). The EuroQol health evaluation is a score between 0 the worst imaginable health state and 100 the best imaginable health state. The third secondary outcome is the Hospital Anxiety and Depression Scale (HADS) which is split up in 7 items of which the sum leads to a depression score and 7 items of which the sum leads to an anxiety score. A score of 0 to 7 for either subscale was regarded as in the normal range, a score of 11 or higher indicating probable presence of a mood disorder, and a score of 8 to 10 being suggestive of the presence of the state. For missing values we used as an imputed value the mean value of non-missing items if at least half the items in the HADS anxiety or depression

questionnaire has been completed.

All these secondary outcomes were assessed at baseline, 3, 6, 9, 12, 15 and 18 months. An intention to treat analysis of each secondary outcome was undertaken using mixed models with variation between patients and variation between occasions nested within patients treated as random effects. This analysis was done to estimate the difference in slopes between patients randomised to placebo and LiCO3. This difference was then re-estimated in a model adjusting for the difference between centres and sites of disease onset. Patients in the study belonged to 10 different centres and could have limb or bulbar as site of onset.

Each secondary outcome was also modelled jointly with the time to death using methods described by Henderson, Diggle and Dobson (2000). The survival data will be analysed using a Cox proportional hazards model incorporating random effects. Functional outcomes will be modelled using mixed models taking into account the repeated measures. A key feature of each of these models is that within each of them it is possible to fit a latent variable that can be conceptualised as the patient's propensity to experience poor outcomes (in the context of survival analysis this is usually referred to as frailty). It is the inclusion of this latent variable that allows us to adjust our estimates of the treatment effect to allow for the different rates of drop out in each group. Both models will be estimated simultaneously; parameter estimates will be based on maximising the joint likelihood over both the survival and repeated measures data. SE and confidence limits were calculated using 100 bootstrap samples. The joint analysis was done with and without adjusting for randomisation strata.

The analysis was undertaken in R 2.11.1 using the package nlme for the longitudinal models and the package joineR (made available by Pete Philipson) for the joint models.

See Appendix 3 for a list of statistical results.

The analytic strategy is to compare the rate of change in the two study groups (estimate of β_3 in Model A to D). In the basic unadjusted analysis for the ALSFRS-R the annual rate of change was -9.31 in the placebo group and -9.50 in the $LiCO_3$ group. The difference between these rates was not statistically significant -0.19 (95% CI -1.28, 0.90). Upon inspection it was observed that the rate of decline was greater in patients who did not survive until 18 months (Figure 2 and Tables 38 and 39). This was confirmed when the survival data and longitudinal date were jointly modelled. As part of the modelling the association between the longitudinal and survival components is estimated (this is the parameter γ in the models specified in the appendix). In the analysis of ALSFRS-R the estimate of γ, was -0.13 (95% CI -0.17,-0.10). A negative value of γ implies that a lower current value of ALSFRS-R score (patients who are worse) leads to a greater risk of death. Based on the joint modelling the rate of change in ALSFRS-R adjusted for survival was -9.47 in the placebo group and -9.75 in the $LiCO_3$ group. As before, the difference between these rates of decline was not statistically significant; difference = -0.28 (95% CI -2.40, 1.67). In both sets of analyses (separate and joint) adjusting for randomisation strata had little impact on the point estimates of annual change; the confidence intervals were a little wider.

In the unadjusted analysis for the EQ5-D health state tariff the annual rate of change was -0.26 in the placebo and -0.29 in the $LiCO_3$ group, the difference -0.03 (95% CI -0.08, 0.02) was not statistically significant. The rate of decline was greater in patients who did not survive until 18

months (Figure 2). Jointly modelling the EQ5-D health state tariff and survival data, the difference in rate of change in EQ5-D adjusted for survival was -0.03 (95% CI -0.12, 0.04). γ is estimated as -2.25 (95% CI -3.33, -1.48), which implies that a lower current health state tariff leads to a greater risk of death. In each of these analyses adjusting for randomisation strata has no impact on the annual change, γ changes to -2.59 (95% CI -4.06, -1.74).

In the unadjusted analysis for the EuroQol health evaluation score the annual rate of change was -8.88 in the placebo and -11.83 in the $LiCO_3$ group. The differences between these rates was not statistically significant -2.94 (95%CI -6.49, 0.60). It was observed that the rate of decline was greater in patients who did not survive until 18 months (Table 54). Jointly modelling the EuroQol health evaluation and the survival data, the rate of change in EuroQol adjusted for survival was -9.26 in the placebo group and -12.35 in the $LiCO_3$ group. As before the difference between groups was not statistically significant -3.09 (95% CI -9.78, 1.51). The estimate of γ is -0.03 (95% CI -0.04,-0.01). A negative value of γ implies that a lower current value of EuroQol (patients who are worse) is associated with a greater risk of death. In each of these analyses adjusting for randomisation strata had little impact on the point estimates and confidence intervals of annual change.

In the unadjusted analysis for the HADS anxiety subscale the difference in slopes between patients randomised to $LiCO_3$ and those randomised to placebo is 0.40 which is not significant (95% CI -0.21, 1.00), the annual rate of change was 0.12 in the placebo and 0.52 in the $LiCO_3$ group which is very small compared to the 0-21 range of the total score. The joint model gives very similar results, in this case γ is estimated as 0.05 (95% CI -0.03, 0.09) which is not statistically significant. For the HADS anxiety there doesn't seem to be a significant latent association between the measurements and the events.

In the unadjusted analysis for the HADS depression subscale the annual rate of change was 1.27 for the placebo and 1.53 for the $LiCO_3$ group, the difference 0.26 (95% CI -0.26, 0.78) was not statistically significant. The rate of increase was greater for patients who did not survive until 18 months (Table 54). Jointly modelling the HADS depression and survival data gives similar results with a non-significant difference in slopes of 0.27 (95% CI -0.36, 1.01). γ is estimated as 0.12 (95% CI 0.06, 0.18) which is statistically significant. A positive value of γ implies that a higher current value of HADS depression (patients who are worse) leads to a greater risk of death. In each of these analyses adjusting for randomisation strata had little impact.

Analysis of quality of life: key results

- There was a marked deterioration in functional health status, quality of life and mental health status over time
- The rate of change was greater in patients who did not survive until the end of the study
- The rate of change did not differ significantly between groups

16.0 Conclusion

Across all analyses the observed differences in outcomes between groups was not statistically significant. There is no evidence that treatment with $LiCO_3$increases length of survival in this patient population.

Appendix 1: Concomitant Medication

The following courses of medication were included in the concomitant medication log.

TABLE 41: COURSE OF CONCOMITANT MEDICATION BY TREATMENT ALLOCATION

			TrialArm		
			A	B	Total
Body system	Cardiovascular	Count	113	136	249
		% within TrialArm	10.2%	11.1%	10.7%
	Respiratory	Count	109	105	214
		% within TrialArm	9.8%	8.6%	9.2%
	Hepatic	Count	3	1	4
		% within TrialArm	.3%	.1%	.2%
	Gastro-intestinal	Count	147	178	325
		% within TrialArm	13.2%	14.6%	13.9%
	Genito-urinary	Count	43	41	84
		% within TrialArm	3.9%	3.4%	3.6%
	Endocrine	Count	21	17	38
		% within TrialArm	1.9%	1.4%	1.6%
	Haematological	Count	17	33	50
		% within TrialArm	1.5%	2.7%	2.1%
	Musculo-skeletal	Count	165	202	367
		% within TrialArm	14.9%	16.5%	15.7%
	Neoplasia	Count	0	1	1
		% within TrialArm	.0%	.1%	.0%
	Neurological	Count	226	212	438
		% within TrialArm	20.4%	17.3%	18.8%
	Psychological	Count	51	55	106
		% within TrialArm	4.6%	4.5%	4.5%
	Immunological	Count	37	44	81
		% within TrialArm	3.3%	3.6%	3.5%
	Dermatological	Count	29	26	55
		% within TrialArm	2.6%	2.1%	2.4%
	Allergies	Count	4	7	11
		% within TrialArm	.4%	.6%	.5%
	Eyes	Count	40	55	95
		% within TrialArm	3.6%	4.5%	4.1%
	Food Supplement	Count	49	41	90
		% within TrialArm	4.4%	3.4%	3.9%
	Homeopathic	Count	39	43	82
		% within TrialArm	3.5%	3.5%	3.5%
	Herbal	Count	15	19	34
		% within TrialArm	1.4%	1.6%	1.5%
	Other	Count	2	6	8
		% within TrialArm	.2%	.5%	.3%
Total		Count	1110	1222	2332
		% within TrialArm	100.0%	100.0%	100.0%

Each course of medication is classified as to whether the medication is ALS related.

TABLE 42: COURSE OF MEDICATION BY WHETHER RELATED TO ALS

			ALS related?		
			No	Yes	Total
Body system	Cardiovascular	Count	248	1	249
		% within Body system	99.6%	.4%	100.0%
	Respiratory	Count	160	54	214
		% within Body system	74.8%	25.2%	100.0%
	Hepatic	Count	4	0	4
		% within Body system	100.0%	.0%	100.0%
	Gastro-intestinal	Count	255	70	325
		% within Body system	78.5%	21.5%	100.0%
	Genito-urinary	Count	84	0	84
		% within Body system	100.0%	.0%	100.0%
	Endocrine	Count	37	1	38
		% within Body system	97.4%	2.6%	100.0%
	Haematological	Count	50	0	50
		% within Body system	100.0%	.0%	100.0%
	Musculo-skeletal	Count	200	167	367
		% within Body system	54.5%	45.5%	100.0%
	Neoplasia	Count	0	1	1
		% within Body system	.0%	100.0%	100.0%
	Neurological	Count	61	377	438
		% within Body system	13.9%	86.1%	100.0%
	Psychological	Count	73	33	106
		% within Body system	68.9%	31.1%	100.0%
	Immunological	Count	81	0	81
		% within Body system	100.0%	.0%	100.0%
	Dermatological	Count	55	0	55
		% within Body system	100.0%	.0%	100.0%
	Allergies	Count	11	0	11
		% within Body system	100.0%	.0%	100.0%
	Eyes	Count	73	22	95
		% within Body system	76.8%	23.2%	100.0%
	Food Supplement	Count	80	10	90
		% within Body system	88.9%	11.1%	100.0%
	Homeopathic	Count	55	27	82
		% within Body system	67.1%	32.9%	100.0%
	Herbal	Count	34	0	34
		% within Body system	100.0%	.0%	100.0%
	Other	Count	5	3	8
		% within Body system	62.5%	37.5%	100.0%
Total		Count	1566	766	2332
		% within Body system	67.2%	32.8%	100.0%

Appendix 2: Evaluation of blinding

Clinicians guesses corresponded with 140 patients:

TABLE 43: CLINICIAN GUESS & TREATMENT ALLOCATION

Clinician guess * Treatment allocation

Count

		Treatment allocation		
		Control	$LiCO_3$	Total
Clinician guess	I strongly think he/she was prescribed active medication	1	6	7
	I think he/she was prescribed active medication	35	36	71
	I think he/she was prescribed placebo	35	22	57
	I strongly think he/she was prescribed placebo	5	0	5
Total		76	64	140

Those clinicians who had a strong view were generally correct. Those who were unsure were less likely to be correct.

Appendix 3: Summary statistics

The number of observations at each time point and mean scores for each of the secondary outcomes are given in the following tables:

TABLE 44: NUMBER OF ALSFRS-R OBSERVATIONS PER TRIAL ARM AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	107	103	94	85	78	69	59
$LiCO_3$	107	95	92	79	68	52	47
Total	**214**	**198**	**186**	**164**	**146**	**121**	**106**
Missing	0	10	9	19	16	15	11
Missing (deceased)	0	6	19	31	52	78	97

TABLE 45: MEAN (SD) OF ALSFRS-R SCORE AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	38.64 (5.72)	35.27 (8.09)	33.43 (8.74)	32.13 (8.42)	30.20 (8.90)	28.88 (9.14)	28.54 (9.27)
$LiCO_3$	38.20 (5.66)	36.17 (6.65)	32.40 (8.24)	30.04 (8.55)	28.31 (9.50)	29.47 (10.23)	29.32 (9.96)
Total	**38.42 (5.68)**	**35.70 (7.43)**	**32.92 (8.49)**	**31.12 (8.52)**	**29.32 (9.20)**	**29.13 (9.58)**	**28.89 (9.54)**

TABLE 46: NUMBER OF EQ5-D OBSERVATIONS PER TRIAL ARM AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	107	101	94	84	77	69	57
$LiCO_3$	107	96	92	80	68	51	47
Total	**214**	**197**	**186**	**164**	**145**	**120**	**104**
Missing	0	11	9	19	17	16	13
Missing (deceased)	0	6	19	31	52	78	97

TABLE 47: MEAN (SD) OF EQ5-D SCORE AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	0.59 (0.28)	0.50 (0.31)	0.46 (0.34)	0.42 (0.33)	0.37 (0.34)	0.33 (0.32)	0.33 (0.35)
$LiCO_3$	0.59 (0.30)	0.54 (0.35)	0.42 (0.38)	0.35 (0.35)	0.30 (0.38)	0.32 (0.39)	0.30 (0.40)
Total	**0.59 (0.29)**	**0.52 (0.33)**	**0.44 (0.36)**	**0.39 (0.34)**	**0.33 (0.36)**	**0.33 (0.35)**	**0.32 (0.37)**

TABLE 48: NUMBER OF EUROQOL OBSERVATIONS PER TRIAL ARM AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	107	102	94	85	78	67	58
$LiCO_3$	107	96	93	81	65	50	47
Total	**214**	**198**	**187**	**166**	**143**	**117**	**105**
Missing	0	10	8	17	19	19	12
Missing (deceased)	0	6	19	31	52	78	97

TABLE 49: MEAN (SD) OF EUROQOL SCORE AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	70.07 (19.48)	63.74 (22.32)	64.89 (20.21)	64.60 (21.31)	61.97 (21.36)	59.43 (21.74)	61.95 (23.97)
$LiCO_3$	68.50 (18.50)	64.09 (22.22)	61.17 (21.37)	60.14 (21.11)	57.03 (24.48)	56.40 (24.07)	56.36 (22.86)
Total	**69.28 (18.97)**	**63.91 (22.21)**	**63.04 (20.82)**	**62.42 (21.26)**	**59.73 (22.88)**	**58.14 (22.72)**	**59.45 (23.53)**

TABLE 50: NUMBER OF HADS ANXIETY OBSERVATIONS PER TRIAL ARM AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	107	102	94	85	78	69	58
$LiCO_3$	107	96	92	80	67	51	47
Total	**214**	**198**	**186**	**165**	**145**	**120**	**105**
Missing	0	10	9	18	17	16	12
Missing (deceased)	0	6	19	31	52	78	97

TABLE 51: MEAN (SD) OF HADS ANXIETY SCORE AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	4.46 (3.76)	4.33 (3.62)	4.19 (3.76)	4.53 (3.86)	4.67 (4.05)	4.54 (4.03)	3.50 (3.54)
$LiCO_3$	4.59 (3.37)	5.03 (4.19)	5.30 (4.08)	5.09 (3.90)	5.96 (4.42)	5.26 (4.05)	4.55 (4.26)
Total	**4.52 (3.56)**	**4.67 (3.91)**	**4.74 (3.95)**	**4.80 (3.88)**	**5.26 (4.26)**	**4.84 (4.03)**	**3.97 (3.90)**

TABLE 52: NUMBER OF HADS DEPRESSION OBSERVATIONS PER TRIAL ARM AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	107	102	94	85	78	69	58
$LiCO_3$	107	96	92	80	67	51	47
Total	**214**	**198**	**186**	**165**	**145**	**120**	**105**
Missing	0	10	9	18	17	16	12
Missing (deceased)	0	6	19	31	52	78	97

TABLE 53: MEAN (SD) OF HADS DEPRESSION SCORE AT EACH TIME POINT

Trial arm	0 months	3 months	6 months	9 months	12 months	15 months	18 months
Placebo	4.00 (3.10)	4.36 (3.06)	4.53 (3.65)	4.74 (3.30)	5.05 (3.62)	5.67 (3.96)	4.71 (3.76)
$LiCO_3$	3.89 (2.84)	4.83 (3.32)	5.61 (3.66)	5.80 (3.45)	5.88 (3.60)	5.03 (3.60)	5.17 (3.92)
Total	**3.94 (2.97)**	**4.59 (3.19)**	**5.06 (3.69)**	**5.25 (3.40)**	**5.43 (3.63)**	**5.40 (3.81)**	**4.91 (3.82)**

Rate of change in functional health status, quality of life and mental health state

TABLE 54: SEPARATE LONGITUDINAL ANALYSIS

Annual rate of change in quality of life – Separate longitudinal analysis

	Unadjusted						Adjusted for randomisation strata					
	Control		$LiCO_3$		Difference		Control		$LiCO_3$		Difference	
Measure	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95% CI**
ALSFRS-R	-9.31	-10.05, -8.58	-9.50	-10.31, -8.70	-0.19	-1.28, 0.90	-9.31	-10.04, -8.57	-9.52	-10.32, -8.71	-0.21	-1.30, 0.88
HADS anxiety	0.12	-0.28, 0.53	0.52	0.07, 0.96	0.40	-0.21, 1.00	0.13	-0.28, 0.53	0.52	0.08, 0.97	0.40	-0.21, 1.00
HADS depression	1.27	0.92, 1.62	1.53	1.15, 1.91	0.26	-0.26, 0.78	1.27	0.92, 1.62	1.54	1.16, 1.93	0.27	-0.25, 0.79
EQ5-D	-0.26	-0.29, -0.22	-0.29	-0.32, -0.25	-0.03	-0.08, 0.02	-0.26	-0.29, -0.22	-0.29	-0.33, -0.25	-0.03	-0.08, 0.02
EuroQol	-8.88	-11.28, -6.48	-11.83	-14.44, -9.21	-2.94	-6.49, 0.60	-8.88	-11.27, -6.48	-11.97	-14.58, -9.36	-3.10	-6.64, 0.45

TABLE 55: JOINT MODELLING WITH SURVIVAL DATA

Annual rate of change in quality of life – After joint modelling with survival data

	Adjusted only for survival						Adjusted for survival and randomisation strata					
	Control		$LiCO_3$		Difference		Control		$LiCO_3$		Difference	
Measure	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95%CI**	**μ**	**95% CI**
ALSFRS-R	-9.47	-10.98, -8.46	-9.75	-11.62, -8.47	-0.28	-2.40, 1.67	-9.44	-10.93, -8.44	-9.74	-11.57, -8.44	-0.30	-2.43, 1.69
HADS anxiety	0.15	-0.29, 0.68	0.55	-0.11, 1.15	0.41	-0.40, 1.02	0.14	-0.30, 0.68	0.54	-0.12, 1.15	0.40	-0.40, 1.02
HADS depression	1.31	0.87, 1.79	1.58	1.08, 2.04	0.27	-0.36, 1.01	1.31	0.87, 1.81	1.60	1.09, 2.07	0.29	-0.33, 1.02
EQ5-D	-0.26	-0.33, -0.22	-0.30	-0.36, -0.24	-0.03	-0.12, 0.04	-0.26	-0.33, -0.22	-0.30	-0.36, -0.24	-0.04	-0.12, 0.04
EuroQol	-9.26	-13.54, -6.80	-12.35	-17.93, -7.86	-3.09	-9.78, 1.51	-9.21	-13.46, -6.73	-12.49	-18.20, -8.00	-3.29	-9.86, 1.30

Appendix 4: Protocol amendments history:

Substantial amendments:

Substantial amendment 1 Approved 20 May 2009
(Ethics (MHRA for information only)
Reasons for amendment:

- To correct the e mail contact details for the Chief Investigator
- To specify a blood test for trial medication levels at baseline
- To define the blood tests that will be used to monitor safety
- To specify that a physician is responsible for doing the neurological exam prerandomisation
- To clarify the arrangements for Lithium (unblinded) and treating (blinded) physicians
- To insert a document history as an appendix.
- MHRA were notified that the person responsible for QP release has changed - that's been sub-contracted to Dr Peter Vogel. The original CTA application lists the site where the QP certifies batch release as Haupt-Pharma Brackenheim GmBH, and that hasn't changed. The responsibility for QP release remains with Haupt-Pharma Brackenheim GmBH.

Substantial amendment 2 Approved 6 October 2009
(Ethics (MHRA for information only)
Reasons for amendment:

- Clarification of haematological markers
- To clarify when safety (lithium) blood tests are to be drawn.
- Update the contact details at the Joint Clinical Trial Office, who has taken on the Sponsor's safety reporting responsibilities to the MHRA.
- Amendment of contact details for Sponsor contact. This is now Ms Jackie Pullen rather than Professor Peter McGuffin
- To include new information in the PIS and protocol about the USA and Canada announced on 23rd September 2009 that a North American trial of lithium carbonate in people with ALS/MND would stop early and that is no significant concerns with regards the safety of LiCALS.
- To seek approval for a standard cover letter to go to all patients along with the PIS explaining the situation with the US/Canadian study as it is felt inappropriate to send the revised PIS out 'cold' without an explanatory cover letter.

Substantial amendment 3 Approved 31st December 2009
Ethics (MHRA for information only)
Reasons for the amendment:

- Extend LICALS recruitment timelines by 4 months (to March 2010)
- Closure of Italian Lithium Trial; TSC/ DMEC had no safety concerns on review of the LICALS data and unanimously agree that the trial remain open.

CONFIDENTIAL
LICALS Trial MHRA Annual Safety Report Page 13 of 13
Date 09 January 2012

Substantial amendment 4
Ethics (MHRA for information only)
Dated 6th May 2010, Approved 22nd June 2010
Reasons for the amendment:

- Change in legal representative Professor Peter McGuffin to Professor Shitij

Kapur.

- To detail changes to Chief Investigator personnel, of the open label extension and inform details of recruitment extension from 31st March 2010 and 30th April 2010.
- To inform you of the transfer of Chief Investigator duties and responsibilities from Professor Nigel Leigh to Professor Ammar Al-Chalabi as of 01 July 2010.
- To extend recruitment for the double blind section of the study from 31st March 2010 to 30th April 2010.
- Decreasing the frequency of pregnancy tests in the double blind study.
- Detail the procedures and assessments of the open label extension study.

Substantial amendment 5
Ethics and MHRA
Dated 2nd August 2010, Approved 29 Nov 2010
Reasons for the amendment:

- To include lithium citrate formulation for PEG patients
- To clarifying dosing regime
- Reduce the open label the timelines from month 18 to month 15; starting in Dec 2010 and closing March 2012.
- To change the primary analysis method for the double blind i.e. from Fisher's Exact to Kaplan Meier.
- Include open label patient information sheet version 1, 2nd August 2010.

Amendment 6 - Non-substantial 1
Protocol version 8, dated 14 December 2010 Ethics approved 3 February 2011
Reasons for the amendment:

- To inform the Ethic of the deputising of Dr Tahir Majeed at the Preston site.
- Administrational changes to OLE assessment scheduled; ECGs and pregnancy test to reflect the visit schedule.

Appendix 5: Template Participant Information Sheet and Informed Consent

[PRINT ON HOSPITAL HEADED PAPER]

LiCALS
PIS Version 1.2, Date: 17 April 2009

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

STUDY TITLE:

A double-blind randomised controlled trial of Lithium Carbonate in Amyotrophic Lateral Sclerosis (LiCALS).

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

This information sheet is in 2 parts:

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you'd like more information – our contact details are at the end of this leaflet. Take time to decide whether or not you wish to take part.

In the United Kingdom Amyotrophic Lateral Sclerosis (ALS) is more commonly known as Motor Neurone Disease (MND) and therefore the term MND will be used throughout this Information Sheet. This Information Sheet has been reviewed by the UK Motor Neurone Disease Association (MND Association) charity — you can phone them (08457 626262), or look on their website (www.mndassociation.org) for further information about MND.

PART 1

What is the purpose of the study?

This study will investigate a possible new treatment for Motor Neurone Disease (MND). The study drug, Lithium Carbonate (in varying doses, aiming to achieve blood levels of 0.4-0.8 mmol/L) is used to treat manic depression (bipolar disorder), depression, mania, self-harming, and aggressive behaviour. Some recent research has suggested that it might also be effective in slowing the progression of MND symptoms. This is a research study; Lithium Carbonate is not currently used to treat MND. The study drug has been prepared as Lithium Carbonate, where the element Lithium is the active ingredient.

In a mouse model of MND, Lithium may be able to stop nerve cells from degenerating. Lithium reduces the activity of an enzyme which is widespread within the cell — by doing that, researchers believe that the study medicine might affect the speed at which nervous impulses are transmitted, and therefore improve the functioning of nerve cells.

The results in mice led researchers in Italy to do a small study involving 44 MND patients. All 44 patients were taking riluzole, the current standard treatment for MND. Sixteen of these patients were given Lithium Carbonate (in the doses which will be used in this study) in

addition to their riluzole, while the remaining 28 took only riluzole. After 15 months, no patients in the group treated with Lithium had died (i.e., 100% survival), compared with a survival rate of 71% in the riluzole-only group. There was also a difference in survival rates at 12 months, and differences in the rate of functional muscle deterioration, lung function, breathing difficulties, and quality of life. However, this study was carried out in a very small number of patients and there were a number of problems with the design of the trial which may have resulted in false positive results. We therefore need to do this study to confirm the findings in a larger number of patients.

We'll look at whether Lithium Carbonate has any effect on your MND symptoms, especially your ability to carry out activities of daily living, and we'll collect information on the side effects of Lithium Carbonate when used to treat people with MND — please see the "What are the risks of taking the study medicine?" section on Page 7.

This is a placebo-controlled study. In total, there'll be 220 participants in the study — 110 will receive the test drug, Lithium Carbonate, and the remaining 110 will receive placebo (a dummy medicine that looks exactly like Lithium Carbonate — you won't be able to tell whether you are taking Lithium Carbonate, or the placebo). The medical team will need to carefully balance the levels of Lithium in your blood – too little and there will be no pharmacological effect, too much and it could be toxic. From the levels used for other conditions (mentioned above), they will keep the levels of Lithium between 0.4 – 0.8mmols/L in this study. It's important for you to realise that your doctor won't be allowed to tell you whether you are taking Lithium Carbonate or the dummy medicine, even if you ask them. A computer will decide at random whether you'll take the Lithium Carbonate or placebo — you'll have a 1 in 2 chance of taking the study medicine (like tossing a coin).

You'll carry on taking riluzole, which is the only medicine currently licensed within the UK to treat MND, so you'll still have access to an active medicine for the treatment of MND.

Why have I been invited?

You have been asked to consider participating in this study because you've been diagnosed with MND and have experienced your first MND symptoms within the last 3 years. There will be ten research centres in the UK recruiting approximately 22 participants each. In total 220 participants will be recruited into this study in the UK.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Your normal care for MND will not be affected in any way by your decision. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You can withdraw at any time and without giving a reason. That won't affect the standard of care you receive.

What will happen to me if I take part?

The study will last about one and a half years (18 months), and you'll be cared for by a medical team. After signing the Consent Form, you'll have some tests and be asked some questions at a screening visit. At the screening visit, we'll ask you to blow into mouthpiece or a mask, so we can measure how well your lungs are working. We'll ask you about your medical history, any drugs you are taking, give you a medical examination, do an electrocardiogram (ECG) (a painless test which measures the electrical activity of the heart), and do a blood test. If you're a woman who is able to have a baby, we'll do a urine pregnancy test at this visit, and on all of your subsequent visits to the clinic. After the screening visit, if your medical team feels that the study is suitable for you, you'll receive your medication (Week 0).

You'll then see the medical team every week for the first 4 weeks (Weeks 1-4), and at Week 8 and Week 12 (Month 3). After that you'll need to come to the clinic every 3 months for the rest of the study — in total, you'll have to attend the clinic on up to 13 occasions, including your screening visit. At each of those visits, we'll do a blood test, to measure your kidney and thyroid function, or to measure the levels of study medication. Depending on the results of the test, we might need to change the number of tablets you are taking — we'll tell you, in writing, whenever we need to do that. If you can't get to the clinic, a member of the research team will contact you by telephone to assess your progress, and you may have the blood tests done at your GP surgery.

The neurological exam we'll do in this study is the same exam as you might have as part of your standard medical care. We'll measure your blood pressure and height, assess your muscle strength and ask you questions about; how easy you find it to do everyday tasks, your mood, and your quality of life.

You'll have up to 13 visits to the clinic during the study, and up to 13 routine blood tests during the study (additional safety bloods maybe required if your condition changes). All of your visits to the clinic will be in the morning, as we will need to measure your Lithium levels when the drug concentration in your bloodstream is at its highest, approximately 12 h after the previous evening's dose.

Will I be paid?

We won't pay you for taking part in the study, but you and your carer will be able to claim back for travel expenses, outside your usual 3 monthly clinic visits.

What do I have to do?

You should swallow the study medication once daily, in the evening, between 9 pm and 10 pm, as directed. If you can't swallow the tablet, please contact your research doctor (if you have a feeding tube, tablets can be crushed to go down it, but this can alter the rate at which the drug is absorbed and more blood tests may be required to achieve blood levels of 0.4-0.8 mmol/L). In considering whether you should be involved in this study, please discuss the need to take extra tablets every day with the person who is likely to support you.

You should contact the clinic if you require further clarification on how to take the tablets, or if you feel any different after you take the study medicine. In case of a suspected overdose, you should stop taking the trial medication immediately, and consult a member of the research team. Please return any unused study medication to the clinic each time you attend for a study visit.

Some other regular medications can react with Lithium Carbonate and may cause raised or lowered levels of Lithium in the blood. Your research doctor will tell you about this in relation to your other regular medication and also about any over the counter drugs which you buy from the pharmacy or other shops. It is important that you keep a record of any changes to your medication and inform your medical team of these changes as soon as possible. If you have any problems with the study medication you should contact your research doctor – contact details are given at the end of this leaflet.

All patients taking part in this study will already be taking riluzole (Rilutek). You should continue to take your riluzole as directed by your doctor throughout the study. You shouldn't change the dose during this study unless instructed to do so by your medical team.

In addition to riluzole, you will also be able to receive standard treatments for relief of your MND symptoms. These symptoms differ from person to person but may include weakness, difficulty with speech or swallowing, problems with drooling of saliva, discomfort, difficulties

sleeping, or occasionally problems with breathing. You should tell the study medical team and the MND team responsible for your day-to-day care about these, and other symptoms you feel are significant and the appropriate treatment will be available as it would if you were not taking part in the trial.

You should not be involved in any other drug trials currently, or have been within 12 weeks prior to screening.

You will need to visit the hospital a total of up to 13 times to see the research team and to undergo assessments. Seven of those visits will coincide with your routine 3-monthly clinic visits, so in total you'll only have to make up to 5 extra visits to the clinic above and beyond your regular appointments, if you do decide to take part. It is important that you attend your scheduled visits at the hospital. If you need to re-schedule your appointment, for example due to holidays, it is important that you let the clinic know so that they can ensure that you have sufficient drug supplies.

What is the drug that is being tested?

The drug being investigated is Lithium Carbonate, a tablet which is used to treat bipolar disorder, depression, mania, self-harming and aggressive behaviour. This study is the first large trial investigating the use of Lithium Carbonate in MND patients.

A varying dose of Lithium Carbonate will be used to achieve and maintain blood levels between 0.4 mmol/l and 0.8 mmol/l. It will be given in the form of tablets to take once a day at night-time.

There are some drugs you shouldn't take whilst taking part in this study because they may interact with Lithium Carbonate, or may affect your MND, making it difficult to measure the performance of the study drug. You'll be asked by the research doctor what drugs you are taking at the beginning of the trial and throughout, and they'll advise you.

What are the alternatives for diagnosis or treatment?

Currently, the only medicine shown to be beneficial in MND is the medicine called riluzole, which you're already taking. This alters the rate at which MND progresses and in a study of people with MND treated with riluzole or placebo over a period of 18 months, those taking riluzole survived on average 3 months longer than those on placebo.

What are the risks of taking the study medicine?

Because Lithium Carbonate has been used in clinical trials and then to treat large numbers of patients for over 100 years, there is a lot of information available about the side effects of the drug.

Lithium Carbonate can cause people to pass urine more frequently and in larger volumes, affect the levels of hormones, raise the levels of calcium and white blood cells in the blood, cause tremors, stomach upset, make a person thirsty, and cause weight gain and swelling.

High levels of Lithium can cause toxicity, early signs of which are blurred vision, increasing stomach upsets (vomiting, diarrhoea), muscle weakness, increased drowsiness and sluggishness increasing to giddiness with poor co-ordination, tremors and slurred speech.

Severe over dosage of Lithium Carbonate requires stopping of medication as this can cause kidney failure, convulsions, raised hormone levels, ECG changes, circulatory failure, psychosis, coma and occasionally death.

The regular blood tests that are carried out monitor the levels that may be affected by the Lithium Carbonate but if you notice any of the above mentioned symptoms which do not resolve spontaneously you should immediately contact a member of your research team using the details at the end of this information sheet. You should also carry your card with details of the emergency 24 hour code break number (Guy's Medical Toxicology Unit, (0)207 358 9167).

What are the other possible disadvantages & risks of taking part?

If you have private health insurance you should check with your provider before agreeing to participate in this clinical trial to ensure that it will not affect your medical cover.

During the study we'll take blood from a vein for laboratory tests. The risks of this procedure include bleeding, infection and slight bruising at the site, which will be minimised by careful and clean techniques. Approximately 15 ml (three teaspoons) of blood will be taken at each visit to the clinic. In total, we'll take under half a pint of blood for the study tests.

Harm to the unborn child

The study treatment might harm the unborn child. So, if you're a woman, you shouldn't take part in this study if you're pregnant, intend to become pregnant during the study, or are breastfeeding. You'll have a pregnancy test before taking part, if you could become pregnant, and on each of your visits. You must agree to use a reliable form of contraception during the trial eg. Hormonal contraception (oral, implants), Intra-Uterine Device (IUD) or two barrier methods e.g. diaphragm with spermicide & condom, during the study, and for at least one month after the treatment has finished.

If you do become pregnant during the course of the study you must tell your study doctor **immediately** so appropriate action can be discussed.

There are no reports in the literature that suggest the use of lithium in men is associated with harm to their partners' unborn child, so extra precautions aren't needed for men taking part in the study.

Harm

In the event that something goes wrong and you are harmed during the research due to someone's negligence then you may have grounds for a legal action for compensation. If the harm is as a result of negligence related to the management of the study, claims would be against the sponsor organisation; King's College London, but you may have to pay your legal costs. The NHS scheme will provide indemnity in respect of negligent harm arising from conduct of the professionals carrying out the research at the site you visit. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What are the possible benefits of taking part?

This is a research study that will help to acquire more knowledge about the use of Lithium Carbonate in the treatment of MND and may be helpful to you or other people worldwide who suffer from the same disease. We cannot promise the study will help you personally but the information we get might help improve treatment of MND in the future.

What happens when the research study stops?

After the study stops all participants will continue to be cared for by the medical team at the hospital, in the same way as they were before the trial. You will continue to have access to

current standard treatment for MND and related symptoms. You will be able to continue taking riluzole, the treatment which is currently licensed for MND.

If the results of the current trial don't indicate otherwise, you will be given the option of entering an open-label trial of Lithium in MND, so you'll be able to continue taking Lithium. If you don't want to be involved in the open-label follow-on trial, you should discuss whether you can continue to take Lithium with your GP.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice. All information about you and your participation in this study will be kept confidential. The details are included in Part 2.

Contact details:

If you require further information about the study or have any concerns during the study please contact *[insert name of study doctor]* Tel No *[insert doctor contact number]*.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

What if relevant new information becomes available?

Sometimes in the course of a research project, new information becomes available about the drug that is being studied. If this happens, your medical team will tell you about it and discuss whether you want to or should carry on in the study. If you decide not to carry on, your medical team will make arrangements for your care to continue in the normal way. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your medical team might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, we will tell you and arrange for your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from treatment without giving any explanation — just tell us. If you wish to stop taking the study medication, you will have the option of continuing to attend for follow-up visits so that we can continue to monitor your progress. If you'd prefer to withdraw from the study completely, we'll ask you to attend the clinic for a final check up. However, you may decline to allow the data from this last visit to be used if you wish. In either case, we'll need to

keep and use information about you collected up to the withdrawal visit. If you withdraw completely, any stored blood samples that can still be identified as yours will be destroyed if you wish.

If you withdraw from study medication, you will also need to return all unused study medication to the clinic, regardless of whether you continue to attend for follow-up visits or withdraw completely.

What if there is a problem?

If you experience any unusual symptoms after taking the study drug, or have any other concerns directly or indirectly related to your participation in this study please contact the research team — contact details are shown at the end of this leaflet.

Complaints:

If you remain unhappy about an aspect of the conduct of this study and wish to complain formally you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital you attend.

Will my taking part in this study be kept confidential?

If you join the study some parts of your medical records and the data collected for the study will be looked at by monitors, auditors, ethics committees, authorised persons from King's College London (the sponsor of this research), UK Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) and representatives of regulatory authorities, to check that the study is being carried out correctly. We may also use the NHS Information Centre for health and social care as part of follow-up. We'll need to provide them with your full name and date of birth, and possibly your address, to do that. All will have a duty of confidentiality to you as a research participant. Any records identifying you will be kept confidential and won't be made publicly available.

Your data will be collected in a paper file and also electronically onto a computer. It will be stored securely and with access restricted to the research team at your hospital and those identified above. Your data will be pooled with data from all other participants in the study and analysed by statisticians to make conclusions about the treatment. The study data will be retained by the sponsor for 15 years after the trial has ended.

Involvement of the general practitioner / family doctor (GP)

Your research doctor will write to your GP to let them know that you are participating in this study.

What will happen to any samples I give?

The blood samples which will be taken during the course of this study will be labelled with your details and hospital number and sent to the hospital laboratories where they will be analysed. Once the analysis has been performed the blood material will be disposed of.

Will any genetic tests be done?

No.

What will happen to the results of the research study?

The results of the study may be published in scientific or medical journals, presented at conferences and/or submitted to regulatory authorities. The results will be shared with you by your research doctor after the last patient completes the study and the analyses have been performed.

You will not be identified in any report or publication.

Who is organising and funding the research?

This study is being organised by the UK Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) MND Clinical Studies Group (CSG) and funded by the MND Association.

The funding provided is paid to *[insert hospital site]* for including you in the study in order to cover your travel expenses.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the South East Research Ethics Committee.

Thank you for taking the time to read this Participant Information Sheet and considering taking part in the research. You may take this Information Sheet away with you to discuss with your family and/or friends. If you decide to participate in the research you will be asked to sign a Consent Form, and will then be given your own copy of your signed Consent Form to keep.

Contact details

Study Doctor: *[insert study doctor name and telephone number]*
Study nurse: *[insert study nurse name and contact telephone number]*

Emergency contact for doctor through switch board of hospital: *[insert hospital switch number]*

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[Print on hospital headed notepaper]

Centre Number: ***[insert centre number]***
Study Number: ***[insert study number]***
Participant ID Number: ***[insert patient ID number]***

CONSENT FORM

Title of Project: A double-blind randomised controlled trial of Lithium Carbonate in Amyotrophic Lateral Sclerosis (LiCALS).

Name of Researcher: *[insert site principal investigator name]*

Please initial the relevant box to confirm your consent.

I confirm that I have read and understand the information sheet, Version 1.2, dated 17 April 2009 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

1. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

2. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from within DeNDRoN, representatives of the sponsor or the NHS trust, the ethics committee and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

3. I agree to my GP being informed of my participation in the study. ☐

4. I understand that information held by the NHS and records maintained by The NHS Information Centre may be used to keep in touch with me and follow up my health status. ☐

5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of Witness (if patient cannot give written consent)	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature

[PRINT ON HOSPITAL HEADED PAPER]

LiCALS
PIS Version 1.2, Date: 17 April 2009

Researcher	Date	Signature

Appendix 6: Deviation Log

Site ID	Centre	Deviation / Violation	Date of D/V	Patient PIN	Parient Initials	Explaination	Date Informed by & Date	Action Required
P01	Bham	Deviation	10-Sep-09	P01002		Early treatment window: month 2 treatment window brought in by a week should be btween 11 to 24 Sept. Brought in to 10 Sept as patient is taking 3 tablets and will be on holiday	Noted during monitoring visit	
P01	Bham	Deviation	10-Sep-09	P01001		Early treatment window: month 2 treatment window brought in by a week should be btween 11 to 24 Sept. Brought in to 10 Sept as patient is taking 3 tablets and will be on holiday	Noted during monitoring visit	
P02	Kings	Violation	14-Sep-09	P02007	ALH	Lithium Blood: Blood drawn on 14 Sept 2009 was taken 4 hours post last dose	16 Sept. 2009	
P02	King's	Deviation	04-Feb-10	P02009	SEM	Patient became pregnant whilst on LICALS trial. Request to break code via Guy Toxixology Unit completed By Prof Chris Shaw (Dircetor Clinical Neuroscience and deptuy PI for KCH)	Blinded RN - Andrew Dougherty	Patient withdrawn from trial medication to continue to attend follow-up visits until month 18. Pregancy terminated
P04	Liverpool	Violation	01-Jul-09	P10001	HMB	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P04	Liverpool	Violation	01-Aug-09	P04002	MMM	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P04	Liverpool	Violation	01-Sep-09	P04003	KJ	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P04	Liverpool	Violation	01-Oct-09	P04005	JH	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P04	Liverpool	Violation	01-Nov-09	P04006	DE	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P04	Liverpool	Violation	01-Dec-09	P04007	PP	Baseline lithium blood not taken	Gemma Wood 8 July 2009	MT informed site via email on 8 Jul09
P06	Newcastle	Deviation	03-Dec-03	P060012	GKP	Patient was admitted to South Tyneside hospital with type 2 respiratory failure. They called the emergency unblinding service as the patient is unconscious and they were concerned to know whether he might have lithium toxicity or if this is MND related. We authorised unblinding, given the circumstances, but asked the registrar to try to keep your team and the patient blind to treatment arm if possible.	Guy CTU to Caroline Murphy 3 Dec. 2009	Site staff not unblinded but pass sadly passed away on 10 Dec. 2009

P06	Newcastle	Deviation	26-Jun-09	P06002	LMW	Screening Biochem Globulin not done	Noted during monitoring visit	Raised descrepancy query - Dr Tim William to request as routine bloods
P06	Newcastle	Deviation	26-Jun-09	P06002	LMW	Screening Biochem Albumin not done	Noted during monitoring visit	Raised descrepancy query - Dr Tim William to request as routine bloods
P06	Newcastle	Deviation	02-Jul-09	P06001	DH	Screening Biochem Globulin not done	Noted during monitoring visit	
P06	Newcastle	Deviation	02-Jul-09	P06001	DH	Screening Biochem Albumin not done	Noted during monitoring visit	
P07	Oxford	Deviation	Nov-09	P07020	RIM	Site arranged for patient to have his blood taken locally on weeks 2 and 3, unfortunately patient and site staff were ublinded by GP	09/12/2009 William. J	Patient withdrawn from trial medication to continue to attend follow-up visits until month 18
P07	Oxford	Deviation	09-Nov-09	P07020	RIM	Site arranged for patient to have his blood taken locally on weeks 2 and 3, unfortunately patient and site staff were ublinded by GP	29 Dec 2012 reported by William J	Has agreed to continue visits and monitoring as per protocol should have his bloods taken as usual today
P08	Plymouth	Deviation	04-Jun-09	P08002	MGV	Thyroid Function test not done at screening	Noted during monitoring visit	Raise decrepancies - Corinna Chambers to requets in furture
P08	Plymouth	Deviation	04-Jun-09	P08002	MGV	Calcium, corrected calium and phosphate all not doen	Noted during monitoring visit	Raise decrepancies - Coriina Chambers to requets in furture
P08	Plymouth	Deviation	4 Nov 2009	P08010	BMB	I have been unblinded to the Lithium status of BMB P08010. This patient's notes have just been returned to us after they were with the neurology department for review. An A4 print out of the result had been placed in the medical notes, which I saw when filing the blood reports from the lab. Christine Cosby has now removed this and has checked for any other results which might have been filed accidentally.	Corina Chambers 4 -11-2009	Patient unaware and continued on study however withdrew from IMP on 4 Dec 2009 - CC has subsquently left the LICALS trial team.
P08	Plymouth	Deviation	Nov-09	P08006	PJ	GP over reacted on the phone to SW	S Wilding	Patient remained on trial
P08	Plymouth	Deviation	22-Oct-09	P08012	JM	Co investigator's email not read by RN	S Wilding	Patient remained on trial
P08	Plymouth	Deviation	19-Aug-09	P08002	MGV	lithium results delivered to Oliver Hanemann	O Hanemann	Patient remained on trial
P08	Plymouth	Deviation	20-Jan-10	P08003	AJD	lithium results were recorded on the PATH system by other departments	O Hanemann	Patient remained on trial
P09	Preston	Deviation	27-Jun-09	P03001	BR	Treatment delay at patient. Last dose of 1 tablet taken on the 27/06/2009.	Noted during monitoring visit	Has agreed to continue visits and monitoring as per protocol should have his bloods taken as usual today