End of Clinical Trial Report

UKATT – UK Amyloidosis **T**reatment **T**rial

1. Trial Summary

EudraCT	2006-006395-37
ISRCTN	ISRCTN34235460
Sponsor No.	BRD/06/055
Sponsor	University College London. Joint UCLH and UCL Biomedical Research Unit, 1st Floor Maple House, 149 Tottenham Court Road.
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CTA Approval	6th September 2007
Main REC Approval	5th July 2007
Current protocol version and date	Version 6.0, 15 December 2008
Full Title	A randomised, multicentre feasibility trial in AL Amyloidosis, comparing CTD with SCT in patients with low risk of Treatment Related Mortality and CTD with Mel-Dex in patients in whom SCT would not be considered appropriate as first line therapy.
Investigational Medicinal Products (IMPs)	Cyclophosphamide Dexamethasone Lenograstrim Melphalan Thalidomide
Treatment Groups	High Intensity Pathway – Cyclophosphamide, Thalidomide and Dexamethasone (CTD) vs High dose melphalan with autologous stem cell support (HDM) Low Intensity Pathway – Cyclophosphamide, Thalidomide and Dexamethasone (CTD) vs Melphalan and Dexamethasone (Mel-Dex)
Target number of patients	48 patients (12 per treatment group)
Final number patients recruited	27 patients (High Intensity Pathway = 1 patient, Low Intensity Pathway = 26 patients – 2 withdrew prior to receiving treatment and were replaced according to the protocol design)

2. Trial Design

The Trial was a randomised, multi-centre, feasibility study conducted in newly diagnosed patients with systemic AL Amyloidosis. Patients entered one of two treatment pathways (high or low intensity) on the basis of their disease, specifically their suitability for Stem Cell Transplant (SCT). Patients in whom intensive high-dose therapy with SCT was considered appropriate as defined by a likelihood of treatment-related mortality of <5% and who met the relevant eligibility criteria entered the High Intensity Pathway; all other patients entered the Low Intensity Pathway and were randomised within each pathway to one of two chemotherapy regimens on a 1:1 basis. Patients eligible for the High Intensity Treatment Pathway were randomised to SCT or (CTD) and those eligible for the Low Intensity Treatment Pathway were randomised to receive either CTD or melphalan, dexamethasone (Mel-Dex).

Patients were recruited and randomised at the UK National Amyloidosis Centre (UKNAC), Royal Free Hospital after being referred for diagnosis, staging and treatment recommendations according to standard NHS practice before being referred back to one of 14 Regional Haematology Centres (RHCs) for treatment. All patients attended the UK NAC for follow up assessments after 3 cycles of chemotherapy (or 3 months after randomisation for patients receiving SCT or less than 3 cycles of chemotherapy) and seven months after randomisation (or in patients receiving a full 6 cycles of chemotherapy; 1 month after the final cycle of treatment). The first patient was registered on 30/01/2008 and the last patient was registered on 20/03/2009.

3. Trial Objectives

The objectives of the trial were to test the feasibility of a Phase III study in patients with newly diagnosed systemic AL amyloidosis at all stages of disease within the UK. Feasibility was defined in terms of recruitment rate and comparing different chemotherapeutic regimens as initial therapy with respect to rate of clonal response, safety and treatment-related mortality and organ response. In addition, quality of life before and after chemotherapy were investigated to assess the validity of the existing quality of life measures for myeloma (EORTC QLQ C30 and MY20 questionnaires) in this patient population. The primary endpoints were clonal response defined according to the IWMG Criteria 2006 and the Amyloidosis Consensus Criteria 2005 (Appendix 1), toxicity and safety (including treatment related mortality) and recruitment rate. The secondary endpoints were acceptability of randomisations, quality of life, amyloidotic organ function and relapse rates.

4. Population

The main inclusion criteria were:

- Aged 18 years or greater.
- Newly diagnosed as having systemic AL amyloidosis who have:
    - Diagnostic Congo red histology confirming amyloid deposits,
    - Immunohistochemical exclusion of AA and TTR amyloidosis, whenever doubt about the diagnosis exists, according to NAC current practice,
    - Exclusion of genetic mutations associated with hereditary amyloidosis whenever doubt about the diagnosis exists, according to NAC current practice,
    - Underlying plasma cell dyscrasia that can be identified and monitored by Freelite serum free light chain assay as follows: absolute serum free light chain concentration ≥50mg/l associated with an abnormal κ / λ ratio. Among patients with a creatinine clearance of <50mls/min, inclusion requires the κ / λ ratio to be either <0.26 or >2.0,
    - Amyloid-related organ dysfunction or organ syndrome.
- Capable of providing written, informed consent.
- Estimated life expectancy of at least 6 months.
- Prepared to use contraception in accordance with (and consent to) the Celgene approved process for Thalidomide Risk Management and Pregnancy Prevention, or commit to absolute and continuous abstinence.

The main exclusion criteria were:

- Overt symptomatic multiple myeloma as evidenced by myeloma related end organ impairment (ROTI) according to the international myeloma working group criteria 2003 but excluding any organ dysfunction caused by AL amyloidosis
- Underlying IgM paraproteinaemia.
- Amyloidosis of unknown or non-AL type.
- Localised AL amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ.
- Trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome (e.g., isolated carpal tunnel syndrome).
- Isolated soft tissue involvement.

- Severe peripheral neuropathy causing significant functional impairment.
- NYHA Class IV heart failure.
- Liver involvement by amyloid causing bilirubin >1.5 times upper limit of normal.
- Previous treatment for systemic AL amyloidosis.
- Previous or concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas.
- Pregnant, lactating or unwilling to use adequate contraception.
- Intolerance / sensitivity to any of the study drugs.

To be eligible for entry into the High Intensity Treatment Pathway, all of the following inclusion criteria had to be met. Where all of the following inclusion criteria were not met entry was into the Low Intensity Treatment Pathway.

- ECOG Performance Status of 0 or 1
- NYHA heart failure class of <3
- No more than 2 organs involved by amyloid by consensus guidelines.
- Age ≤65 years.
- Creatinine clearance ≥50ml/min.
- Bilirubin ≤1.5 times and alkaline phosphatase ≤2 x upper limit of normal.
- Interventricular septum and left ventricular posterior wall thicknesses of ≤15mm by echocardiography.
- Absence of clinically important amyloid-related autonomic neuropathy.
- Absence of clinically important amyloid-related gastro-intestinal haemorrhage.

5. Treatment

HIGH-INTENSITY TREATMENT PATHWAY DETAILS
Patients were randomised to receive either:

- C-Thal-Dex Chemotherapy (CTD) or
- High dose melphalan (HDM) with autologous stem cell support (transplantation)

CTD chemotherapy arm:

Days 1,8,15, 22	Cyclophosphamide 350mg/m^2 limited to a maximum of 500 mg p.o.
Continuously	Thalidomide Pharmion 50mg hard capsules (Thalidomide); initially 100mg daily p.o. for 28 days, increasing to 200 mg daily p.o.
Days 1-4 9-12 and 17-20	Dexamethasone 40mg daily p.o.

The cycle was repeated every 28 days for a minimum of 3 cycles. After the third cycle of CTD, patients continued until they achieved a plateau, a complete response or to a maximum of 6 cycles.

High dose melphalan with autologous stem cell support
HDM was given in two divided doses in accordance with the US protocol for SCT in AL amyloidosis (Appendix 2).

LOW-INTENSITY TREATMENT PATHWAY DETAILS
Patients were randomised to receive either:

- C-Thal-Dex Chemotherapy (CTD) or
- Melphalan and Dexamethasone Chemotherapy (Mel-Dex).

CTD chemotherapy arm

Days 1,8,15, 22	Cyclophosphamide 350mg/m^2 limited to a maximum of 500 mg p.o.
Continuously	Thalidomide Pharmion 50mg hard capsules (Thalidomide); initially 100mg daily p.o. for 28 days, increasing to 200 mg daily p.o.
Days 1-4 9-12 and 17-20	Dexamethasone 40mg daily p.o.

The cycle was repeated every 28 days for a minimum of 3 cycles. After the third cycle of CTD, patients continued until they achieved a plateau, a complete response or to a maximum of 6 cycles.

Mel-Dex chemotherapy arm

Day 1-4:	Oral melphalan 0.22 mg/kg daily.
Day 1-4, 9-12 and 17-20	Dexamethasone 40mg daily p.o if tolerated.

The cycle was repeated every 28 days for a minimum of 3 cycles. After the third cycle, patients continued with chemotherapy until they achieved a plateau, a complete response or to a maximum of 6 cycles.

6. Participant Flow

The sample size was a total of 48 patients (12 patients per treatment group; 24 in the Intensive and 24 in the Non-intensive pathway). This was based on recommendations on the size of pilot studies where there is insufficient prior data on which to base a formal sample size[1] to give sufficient precision around the response rate estimates to inform sample size calculations for the Phase III trial. Patients who withdrew from the trial prior to starting any trial treatment were replaced (the start of trial treatment was defined as first dose of protocol defined chemotherapy in patients randomised to CTD or Mel-Dex and the start of treatment for stem cell mobilisation in patients randomised to SCT).

One patient was registered to the High Intensity Arm of the trial and randomised to receive stem cell transplantation; treatment was discontinued early following a clinical decision due to a decline in renal function. No other patients were registered to this arm of the trial.

Twenty six patients were registered to the Low Intensity Arm of the trial and twenty five were randomised. One patient was replaced prior to randomisation after becoming ineligible for trial treatment upon attending the RHC. Thirteen patients were randomised to receive Mel-Dex and of these, twelve received protocol treatment; one patient died before receiving treatment and was replaced according to the protocol. One patient has been lost to follow up and four patients discontinued treatment. Twelve patients were randomised to receive CTD and all received protocol treatment; of these six discontinued treatment. Please see Figure 1 for further details.

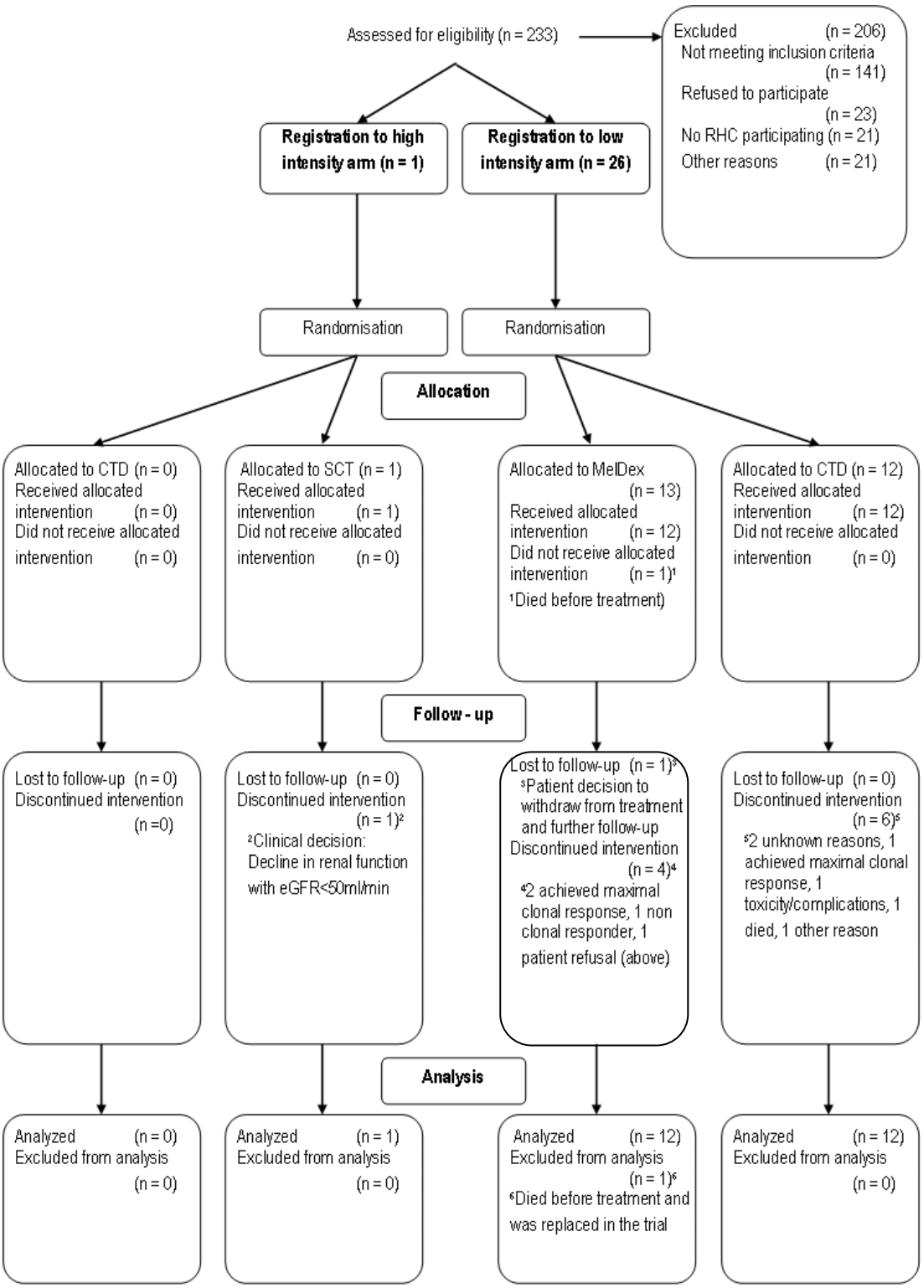

Figure 1

7. Criteria for Evaluation

The primary endpoints were:

- **Clonal Response of the underlying plasma cell dyscrasia** categorised on the basis of the Amyloidosis consensus criteria.
- **Safety** in terms of treatment related mortality, deaths and SAEs by treatment group.
- **Recruitment rate** recorded and displayed monthly for each pathway.

The secondary endpoints were:

- **Acceptability of randomisations** presented as the proportion of patients and doctors who find the trial design or randomisation unacceptable and reasons summarised.

- **Quality of life** scored according to the EORTC QLQ-C30 and QLQ-MY20 questionnaires and including an assessment of appropriateness of use in a further trial for patients with AL amyloidosis.
- **Amyloidotic organ function** and responses categorised according to the Amyloidosis consensus criteria.
- **Relapse rates** listed with duration of response and time from randomisation to relapse.

8. Statistical Methods

The cut off date for the data for analysis was 1st December 2009. All data entered onto the database at this time is included in the analysis. The statistical analysis plan was the responsibility of the CTRU Statistician and was written and agreed prior to the statistical analysis for the trial. For discrete or categorical data, descriptive statistics included tabulations of frequencies and proportions. For continuous data, summary statistics including mean, standard deviation, standard error, median, minimum, and maximum were computed. Time to progression was recorded from time of first treatment. A 95% exact binomial confidence interval was computed for response rates.

9. Results

9.1 Patients and Study Feasibility

Twenty-seven patients were randomised between January 2008 and March 2009. See Figure 1 for the CONSORT diagram for the trial. The high intensity arm was closed after nine months due to lack of recruitment (only one patient was entered). The low intensity arm successfully recruited the required 24 patients. 26 patients were recruited in order to achieve this number as two patients required replacing in the trial according to the protocol. The median age was 67 (range 42 to 85) and stratification was by ECOG performance status which ranged from 0 to 3 (21%, 33%, 33% and 13% of patients respectively. ECOG was matched between the two groups in the low intensity arm.

Detailed records were kept of reasons for patients not entering the trial in order to inform the question of study feasibility and in particular the acceptability of the randomisations. 206 patients were considered for entry into the trial and were not entered. Only four (2%) did not enter the trial due to lack of interest in the study or concerns about the treatment options. The majority of patients were clinically ineligible for the trial (68%); the main reasons being due to receiving previous treatment (16.5%), outlook <6 months (10%), localised amyloidosis (9%), FLC <100 mg/L (8%) or IgM paraprotein (6%). The requirement for FLC >100 mg/L was amended during the trial as it was felt to be overly restrictive.

9.2 Treatment

Of the 24 patients randomised 19 (79%) completed at least 3 cycles of treatment. The median number of cycles (range) was 3 (1 to 5) in the CTD arm and 3 (1 to 6) in the MelDex arm. Four patients (two in each treatment group) stopped treatment prior to the recommended minimum of 3 cycles. One patient achieved maximum clonal response, one patient died, one patient stopped due to toxicity/complications and one patient declined further treatment. The two patients who were replaced in the study withdrew prior to receiving any treatment.

Eleven of the 12 patients (92%) on CTD received routine anticoagulation (6 low dose continuous aspirin and 5 treatment dose warfarin). One patient did not receive anticoagulation in any of their cycles and a further two patients did not receive it in some cycles (reason given ‘not indicated’).

9.3 Deaths

There were no deaths due to treatment complications. There were four deaths in the trial all due to progressive amyloidosis (three in the MelDex group and one in the CTD group). One death (MelDex arm) occurred prior to any treatment, on the day of randomisation. The cause of death in the CTD group was progressive cardiac failure in amyloidotic heart. The causes of death in the MelDex group were progressive renal failure in amyloidotic kidneys, sudden cardiac death in amyloidotic heart and one death was attributed to both progressive cardiac failure and sudden cardiac death.

9.4 Toxicity and Serious Adverse Events

18 (75%) patients experienced grade 3 or 4 toxicity during the trial (10 in the CTD group versus 8 in the Mel-Dex group). The most common toxicities were lethargy (33% of patients), infection (29%) and worsening congestive heart failure or fluid overload (21%).

	Number of events (% of all events)			Number of patients (% of all patients)		
	CTD	**Mel-Dex**	**Overall**	**CTD (n=12)**	**Mel-Dex (n=12)**	**Overall (n=24)**
Constipation	2 (6)	1 (3)	3 (4)	2 (17)	1 (8)	3 (13)
Infection	3 (9)	6 (15)	9 (12)	3 (25)	4 (33)	7 (29)
Lethargy	8 (23)	7 (18)	15 (20)	5 (42)	3 (25)	8 (33)
Pain	5 (14)	5 (13)	10 (14)	2 (17)	2 (17)	4 (17)
Somnolence	1 (3)	0	1 (1)	1 (8)	0	1 (4)
Stomatitis	0	1 (3)	1 (1)	0	1 (8)	1 (4)
Worsening congestive heart failure or fluid overload	5 (14)	4 (10)	9 (12)	3 (25)	2 (17)	5 (21)
Worsening motor neuropathy	1 (3)	0	1 (1)	1 (8)	0	1 (4)
Worsening postural hypotension	1 (3)	0	1 (1)	1 (8)	0	1 (4)
Worsening sensor neuropathy	1 (3)	3 (8)	4 (5)	1 (8)	1 (8)	2 (8)
Other	8 (23)	12 (31)	20 (27)	4 (33)	5 (42)	9 (38)
Total	35	39	74	10 (83)	8 (67)	18 (75)

Table 1: Toxicities – Low Intensity Pathway

There were 25 SAEs in total which occurred in the Low Intensity Pathway; 13(Mel-Dex) and 12(CTD). There were 0 suspected unexpected serious adverse reactions, 10 SAEs deemed suspected to be related to trial treatments Mel-Dex and CTD (5 and 5 respectively); with 15 SAEs deemed not suspected to be related to trial treatments (8 and 7 respectively)

	Mel-Dex	CTD	Total
Number SAEs reported	13	12	25
Relationship to treatment			
• Suspected unexpected	0	0	0
• Suspected expected	5	5	10
• Not suspected	8	7	15

Table 2: SAEs – Low Intensity Pathway

9.5 Clonal Response

This data is not yet available for presentation and will be provided in a follow up to this report.

9.6 Quality of life

Time to complete the questionnaire was 10 minutes on average. The questionnaires appear appropriate for use in the AL amyloidosis population, with only one issue (cramps) raised by a couple of patients that may not be covered in the questionnaires. Full validity of the questionnaires would need to be confirmed in a larger study.

Current guidelines (1) indicate a difference of 5-10 points is a small difference and 10-20 points is of a moderate size when using the QLQ-C30. The questionnaire showed responsiveness over time, with small to moderate differences in some subscales. and show change from baseline graphs for the functional and symptom subscales. Role and social functioning were reduced over the study period (mean 8 and 9.5 points respectively) in the overall study population. Constipation and fatigue were also reduced (7 and 10 points respectively) while pain increased over time (11 points). The meaning of change on the QLQ-MY20 questionnaire is not well known as it is a relatively new questionnaire, however, we observed a reduction in the body image subscale (mean 17 points), an increase in future perspective (mean 7 points), a reduction in disease symptoms (4 points) and increase in side effects (mean 4 points).

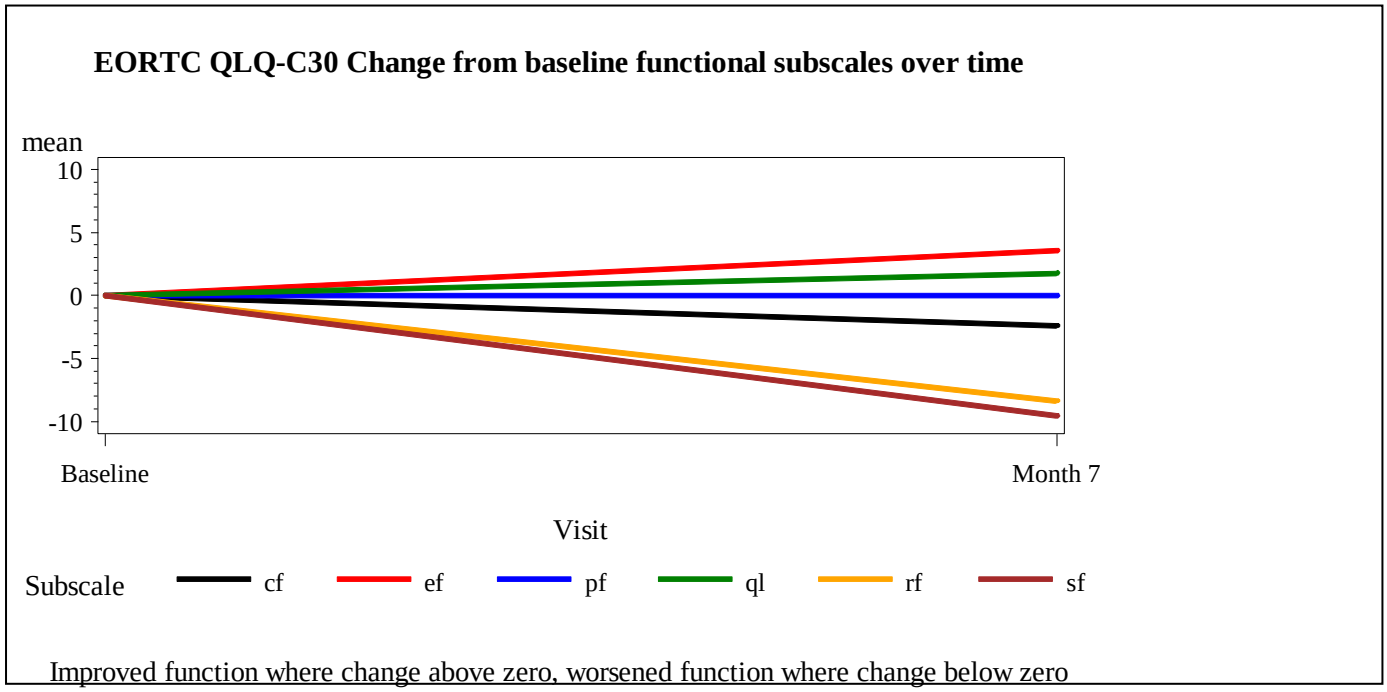

Figure 2 QLQ-C30 change from baseline for functional subscales

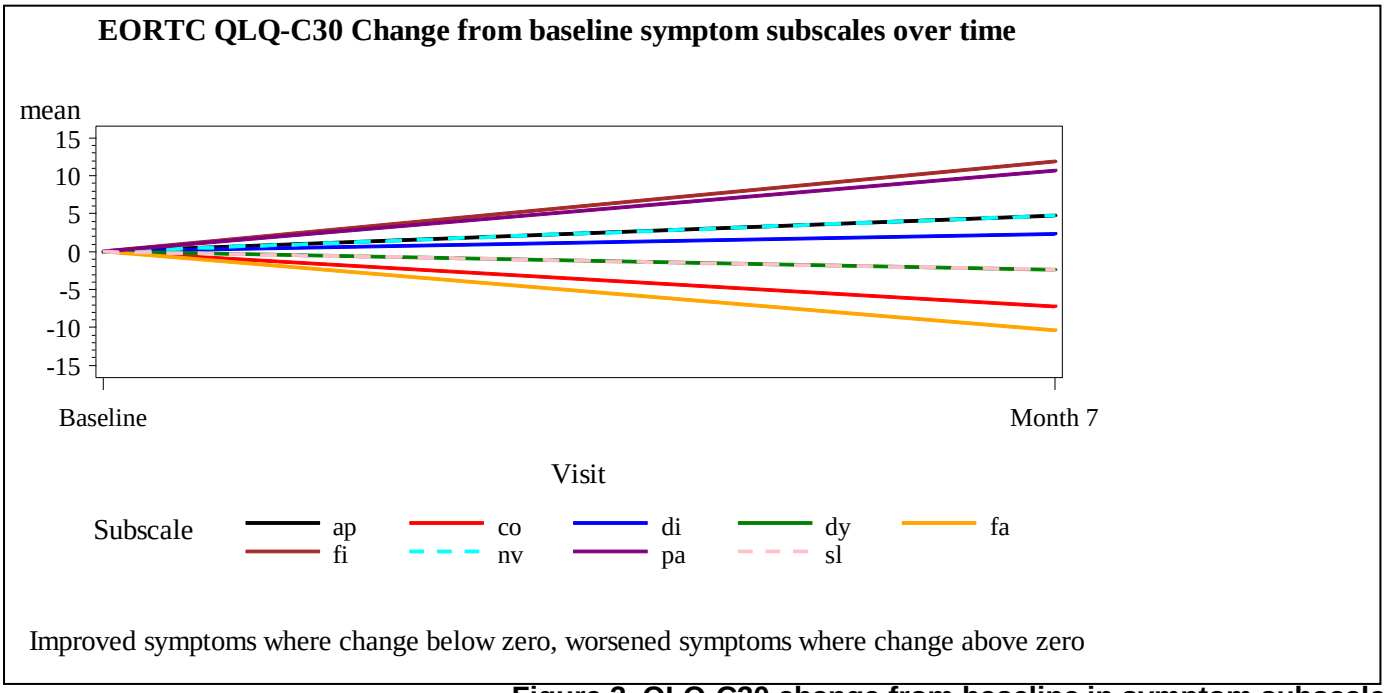

Figure 3 QLQ-C30 change from baseline in symptom subscales

9.7 Amyloidotic organ responses

This data is not yet available and will be provided in a follow up to this report.

10 Amendments

The following substantial amendments to the protocol were made during the trial:

Details	Date MHRA approval	Date Main REC approval
Amendment to eligibility criteria to stipulate that in accordance with the Pharmion Risk Management Programme contraception must start 4 weeks before treatment start date. Original protocol stated contraception must start 2 weeks before treatment start date	18/10/2007	09/11/2007
Amendment to inclusion criteria to permit the use of absolute and continuous abstinence as an approved method of contraception and amendment to the underlying plasma cell dyscrasia. Amendment to exclusion criteria to permit the entry of patients with bone marrow plasmacytosis	20/05/2008	14/04/2008
Closure of High Intensity Treatment Pathway	20/02/2009	13/02/2009

11 References

1. Julious SA. Sample sizes for clinical trials with normal data. Stat Med. 2004;23:1921-1986.

12 Appendices

Appendix 1

DEFINITIONS OF RESPONSE (based on IWMG criteria 2006 and amyloidosis consensus criteria 2005)

Haematological Response:

CR Negative immunofixation of serum and urine (serum alone in anuric patients)

AND

Normal FLC concentration and kappa/lambda FLC ratio (FLC ratio alone in renal failure)

AND

≤5% plasma cells in bone marrow[a] without clonality by immunohistochemistry or immunofluorescence[a]

PR ≥50% decrease in aberrant FLC concentration (or ≥50% change in ratio towards normal if renal failure) but not fulfilling criteria for CR (at six month assessment, ≥50% fall in serum paraprotein required for PR if pre-treatment concentration >10g/L)

NR Not meeting FLC criteria for CR or PR (and/or <50% fall in serum paraprotein at six month assessment if pre-treatment concentration >10g/L).

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; NR, no response.

FLC plateau 3 consecutive FLC samples (each $\geqslant$2 weeks apart) showing the aberrant (monoclonal) light chain concentration to be abnormal but stable (within 20% of each other). In the context of progressive renal impairment, the κ/λ ratio rather than absolute FLC concentration should remain stable (i.e. within 20%).

[a] Confirmation with repeat bone marrow biopsy only if done, not mandatory. Presence/absence of clonal cells is based upon the *k*/λ ratio. An abnormal *k*/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is *k*/λ of >4:1 or <1:2. Alternatively, the absence of clonal plasma cells can be defined based on the investigation of phenotypically aberrant PC. The sensitivity level is 10^{-3} (less than one phenotypically aberrant PC within a total of 1000 PC). Examples of aberrant phenotypes include (1) $CD38^{+dim}$ and $CD56^{+\ strong}$ and $CD19^{-}$ and $CD45^{-}$; (2) $CD38^{+dim}$ and $CD138^{+}$ and $CD56^{++}$ and $CD28^{+}$; (3) $CD138^{+}$, $CD19^{-}$ $CD56^{++}$, $CD117^{+}$.

Haematological Relapse:

From CR Increase in the aberrant serum free light chain concentration outside the normal range and by a factor of ≥2 from that at the time of CR (≥50% change in ratio away from normal in patients with renal failure)

From PR: Increase in the aberrant free light chain concentration by a factor of ≥2 from that at the time of PR (≥50% change in ratio away from normal in patients with renal failure)

Organ Response:

Heart Interventricular septal thickness decreased by 2 mm or 20% improvement in ejection fraction or improvement by 2 New York Heart Association classes without an increase in diuretic use and in the absence of increased wall thickness by >2 mm

Kidney 50% decrease (at least 0.5 g/day) in 24-hr urinary protein loss (urine protein must be >0.5 g/day pretreatment) without fall in creatinine clearance of ≥25% from baseline

Liver 50% decrease in abnormal alkaline phosphatase value or a decrease in liver size radiographically by at least 2 cm

Nerve Improvement in electromyogram nerve conduction velocity (rare)

Soft tissue Definite clinical and/or radiographic improvement with associated functional improvement in affected tissue

Organ Progression:

Heart Interventricular septal thickness increased by >2 mm compared with baseline or an increase in New York Heart Association class by at least 1 grade without an alternative explanation

Kidney 50% increase (at least 1 g/day) in 24-hr urinary protein loss to >1 g/day

OR

Fall in creatinine clearance of ≥25% from baseline

Liver 50% increase of alkaline phosphatase from the lowest value

Nerve Progressive neuropathy by electromyography or nerve conduction velocity

Soft tissue Definite clinical and/or radiographic deterioration with associated functional deterioration in affected tissue

Appendix 2

PROTOCOL FOR HIGH DOSE MELPHALAN ADMINISTRATION

ALL patients should be evaluated clinically for fluid overload before administration of intravenous fluid and monitored by pulse oxymetry throughout the infusion

Patients who are fluid overloaded at the outset should have the fluid infusion regimen reduced from 300ml/hour to 40-100ml/hour

T_2 and T_1 refer to the time of the split doses of melphalan on day -2 and day -1 respectively

Day –2

T_2 minus 2 hour	0.9% Saline @300ml/hour (Total 600ml over two hours)	
Frusemide as needed to keep input = output		
T_2 minus 15 minutes	Dexamthasone	8 mg infusional stat
	Granisetron*	3mg infusional stat
T_2 = 0	Melphalan	100mg/m^2 IVI (5 min in 100 mls)

T_2 plus 5 mins Start 1L 0.9% Saline @300ml/hour and continue to complete 1L infusion (use frusemide as needed)

Day -1

T_1 minus 2 hour	0.9% Saline @300ml/hour (Total 600ml over two hours)	
Frusemide as needed to keep input = output		
T_1 minus 15 minutes	Dexamthasone	8 mg infusional stat
	Granisetron*	3mg infusional stat
T_1 = 0	Melphalan	100mg/m^2 IVI (5 min in 100 mls)

T_1 plus 5 mins Start 1L 0.9% Saline @300ml/hour and continue to complete 1L infusion (use frusemide as needed)

Day 0

T_0 minus 3 hour	0.9% Saline@40-100 ml/hour (depending on fluid status) for 3 hours
$T_0 = T_1$ plus 24 hours	Stem cell re-infusion
T_0 after stem cell re-infusion	0.9% Saline@40-100 ml/hour (depending on fluid status) for 3 hours

ALL patients should have continuous cardiac monitoring during stem cell re-infusion.

ALL patients should have continuous SpO_2 monitoring during stem cell re-infusion adjusting the re-infusion rate to keep stable SpO_2 (ideally >95%)

ALL patients should be on continuous 2L nasal oxygen during and for three hours post stem cell re-infusion

* Or any other suitable anti-emetic.

Signed electronically by Dr Julian Gillmore on 9th November 2010.