

Phase I/II trial of formoterol fumarate combined with megestrol acetate in patients with advanced malignancy

Greig CA¹, Gray C², Johns N¹, MacDonald A¹, Stephens NA¹, Skipworth RJ¹, Wall L³, Fallon M⁴, Price A³, Fox GM⁵, Fearon KCH¹

¹ School of Clinical Sciences and Community Health, University of Edinburgh, UK; ² Clinical Research Imaging Centre, University of Edinburgh;

³ Dept. Clinical Oncology, Western General Hospital, Edinburgh; ⁴ School of Molecular Medicine, University of Edinburgh; ⁵ Acacia Pharma Ltd, Cambridge, UK.



Introduction

- Cancer cachexia treatment is multimodal and must address both reduced food intake and metabolic change (Fig 1).
- Megestrol acetate improves food intake and increases body weight in anorectic cancer patients. Unfortunately the predominant tissue gained is fat.
- β_2 -agonists are known to stimulate muscle protein synthesis but use in humans has been limited by unwanted side-effects (e.g. tremor and palpitations). Formoterol fumarate is a selective β_2 -agonist that can be given orally and has reduced side effects.
- Megestrol acetate and formoterol fumarate have been shown to be effective in animal models (refs 1,2). The present study sought to investigate whether this combination might reverse muscle wasting and improve physical function in cachectic cancer patients.

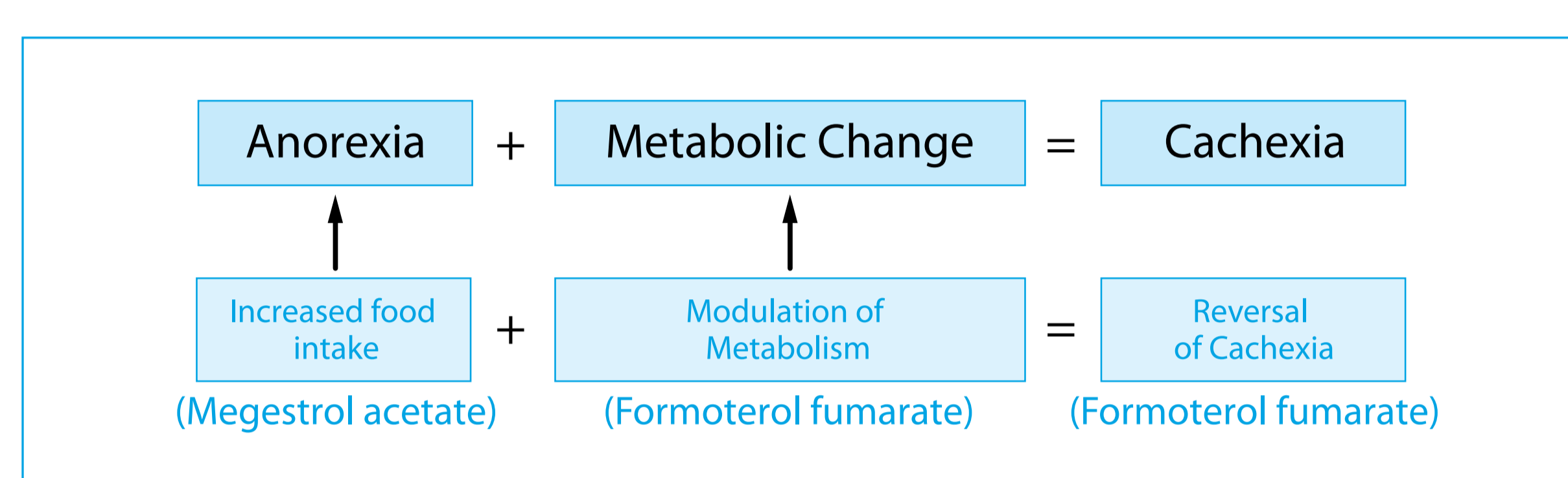


Fig 1: Strategies for intervention in cachexia

Methods

- Thirteen patients (M:F 5:8) with an advanced solid tumour and involuntary weight loss received oral formoterol fumarate (80 μ g/d) and megestrol acetate (480mg/d) for up to 8 weeks.
- We measured quadriceps size by MRI; quadriceps and hand grip strength by dynamometry; lower limb extensor power (LLEP) using a Nottingham Power Rig; and physical activity (PA) by accelerometry (Figs 2 & 3).
- Protocol defined response criteria are shown in Table 1.

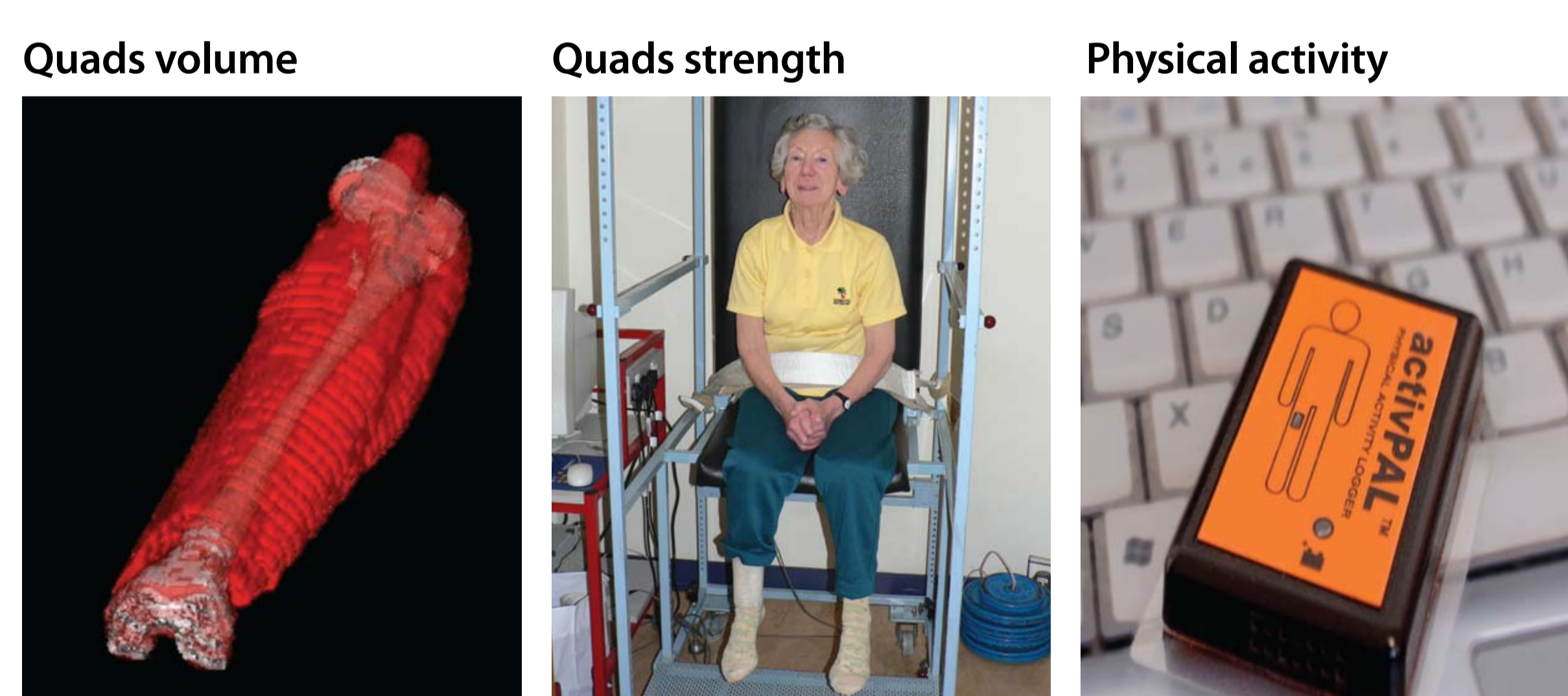


Fig 2: Measurement of muscle size, muscle function and physical activity

Week	Formoterol Fumarate (80 μ g/d) and Megestrol Acetate (480mg/d)		
	0	4	8
Quads CSA	✓		✓
Quads volume	✓		✓
Quads strength	✓	✓	✓
Hand grip strength	✓	✓	✓
LLEP	✓		✓
PA	✓		✓

Fig 3: Study protocol

RESPONSE	Muscle size (quadriceps volume or CSA)	Muscle function (quadriceps strength or power)
	Change compared with baseline	Change compared with baseline
Non-response	Any decline	Any decline
Minor response	0-2%	0-5%
Moderate response	>2% and <4%	>5% and <10%
Major response	\geq 4%	\geq 10%

Table 1: Protocol defined response criteria
Overall major response = major response in either domain

References

1. Busquets S, Figueras MT, Fuster G, Almendro V, Moore-Carrasco R, Ametller E, Argiles JM, Lopez-Soriano FJ. Anticachectic effects of formoterol: a drug for potential treatment of muscle wasting. *Cancer Res.* 2004 Sep 15;64(18):6725-31. 2. Busquets S, Serpe R, Sirisi S, Toledo M, Coutinho J, Martinez R, Orpi M, Lopez-Soriano FJ, Argiles JM. Megestrol acetate: its impact on muscle protein metabolism supports its use in cancer cachexia. *Clin Nutr.* 2010 Dec;29(6):733-7.

Age	Sex	Tumour site	% Weight loss in prior 6 months	PS	Height	Weight	BMI
63	F	Gastric	25.0	1	161	63.5	24.5
75	F	Pancreas	5.2	1	160	60.1	23.5
77	M	Cholangiocarcinoma	12.5	1	187	74.5	21.3
70	M	Oesophageal	15.5	1	180	74.0	22.8
70	F	Pancreas	15.5	1	160	50.0	19.6
83	F	Rectal	14.0	1	146	50.3	25.5
54	F	Gastric	8.0	2	157	41.5	16.8
58	F	Pancreas	8.0	2	154	53.6	22.6
49	F	Cholangiocarcinoma	11.6	1	160	63.7	24.9
73	M	Mesothelioma	13.0	1	164	50.4	18.7
68	F	Pancreas	5.5	1	148	51.0	23.3
61	M	Pancreas	5.0	1	180	62.5	19.3
56	M	Oesophageal	9.5	2	168	78.5	27.8

Table 2: Patient demographics

Results

- All patients had advanced disease (stage 4) and had undergone surgery, chemotherapy or radiotherapy. At baseline, the mean age was 66 years, performance status (PS) was 1 (n=10) or 2 (n=3). Average weight loss was 11.4%, mean BMI was 22.4.

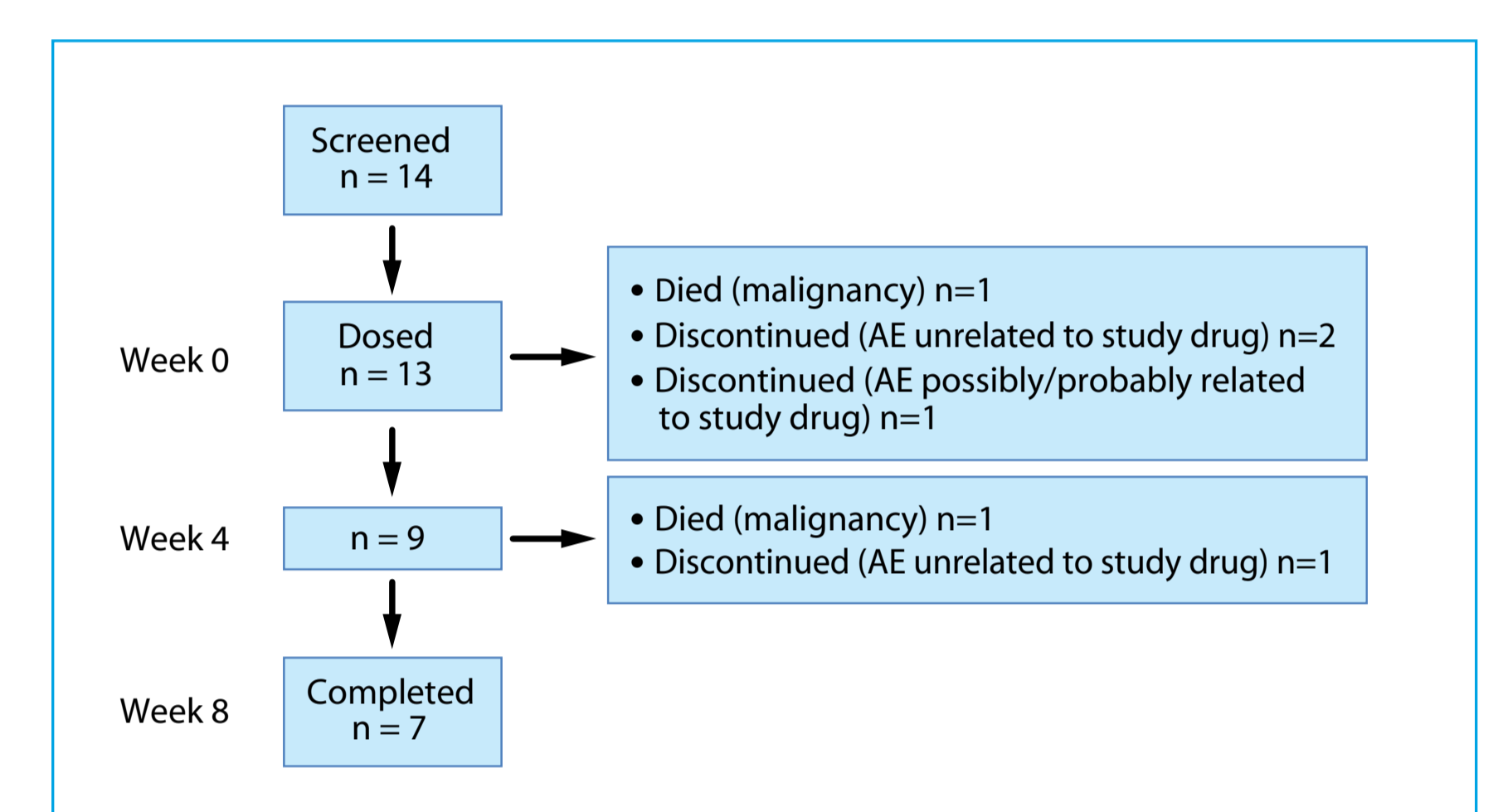


Fig 4: Flow diagram of Patient outcome

- 9/13 patients reached 4 weeks and 7 reached 8 weeks (Fig 4).
- Few adverse events were considered probably or possibly related to study medication; commonest were tremor (8 reports), peripheral oedema (3), tachycardia (2) and heartburn/indigestion (2).
- 6/7 patients had a major response after 8 weeks.

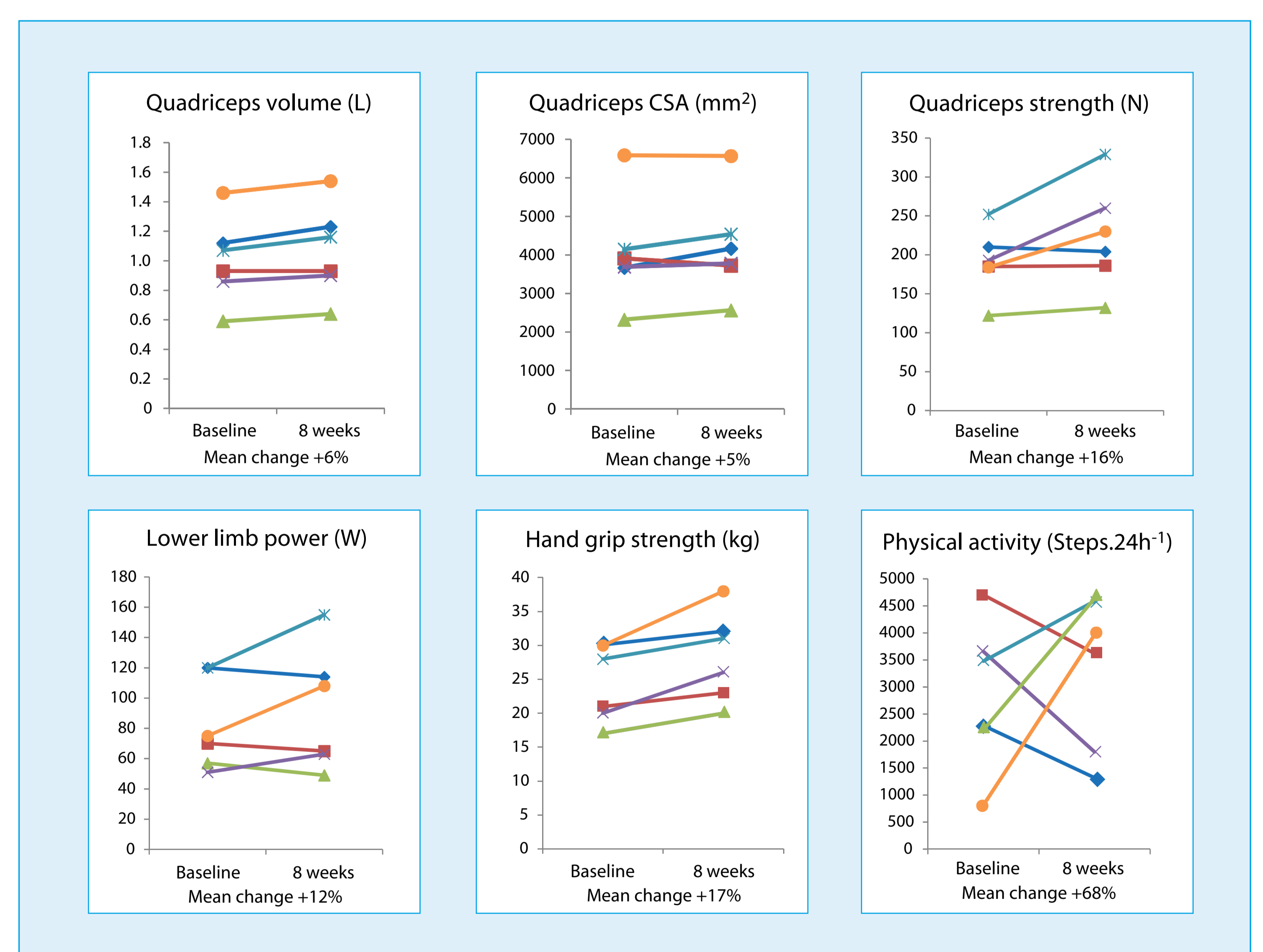


Figure 5: The physiological changes in the major responders at 8 weeks (left limb)

Conclusions

- The present study has demonstrated that the combination of megestrol acetate and formoterol fumarate is well tolerated in frail patients with advanced cancer and cachexia.
- For those patients who reached evaluation at 8 weeks (7/13), a pre-defined overall major response was observed in 6/7.
- The data from this phase I/II study strongly support the further development of megestrol acetate and formoterol fumarate in combination as a treatment for cancer cachexia.

Acknowledgements

We are grateful to Claire Lamb (RGN) and the staff of the Clinical Research Facility, Royal Infirmary Edinburgh.