CLINICAL DEVELOPMENT DEPARTMENT

FINAL STUDY REPORT

Study Number: DC10004

Open-Label, Pilot Phase I/II Study of the Efficacy and Safety of Concomitant Megestrol + Formoterol in Patients with Cachexia and Advanced Malignancy

Investigational Medicinal Product(s)	**Megestrol acetate and formoterol fumarate**	FSR Version	**1.0**
		Date	**01 November 2012**
EUDRACT No	**2008–008857–53**	Principal Investigator	**Prof. Kenneth Fearon**

FINAL STUDY REPORT SUMMARY

Title Open-Label, Pilot Phase I/II Study of the Efficacy and Safety of Concomitant Megestrol + Formoterol in Patients with Cachexia and Advanced Malignancy	
Principal Investigator Prof. Kenneth Fearon	
Study centre Edinburgh Royal Infirmary, 51 Little France Crescent, Edinburgh, EH16 4SA, UK	
Publication Greig CA, Gray C, Johns N, MacDonald A, Stephens NA, Wall L, Fallon M, Price A, Fox GM, Fearon KCH. Phase I/II trial of formoterol fumarate combined with megestrol acetate in patients with advanced malignancy. *J Cachexia Sarcopenia Muscle 2011* Dec;2(4):259-60.	
Study period April 2009-November 2011	**Phase of development** I/II
Objectives The primary objective was to assess efficacy of megestrol and formoterol given concomitantly. The secondary objective was to assess safety of megestrol and formoterol given concomitantly.	
Study design Single-centre, open-label, non-randomised study	
Number of subjects (planned and analysed) Planned: 13–16 Analysed: 13	
Main criteria for inclusion Adult, male and female patients with any advanced solid tumor and ongoing cachexia, excluding weight loss caused by simple starvation	
Investigational Medicinal Products (IMPs) Megestrol acetate tablets (160 mg) for oral administration, daily dose 480 mg in divided doses, for 8 weeks. Formoterol fumarate tablets (40 μg) for oral administration, daily dose 80 μg (40 μg b.d.) for 8 weeks.	
Comparator Product None	

Criteria for evaluation

Efficacy analysis:

All subjects who received at least 4 weeks of study medication were included in the efficacy analysis.

Safety and tolerability:

All subjects who received the study medication, whether prematurely withdrawn from the study or not, were included in the safety analysis.

Statistical and analytical methods

Primary and Secondary Study Variables

The primary study variable was muscle response, defined according to the parameters presented below:

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

The higher of the two outcomes for size and function (or the only outcome, if one is missing) is taken as the overall muscle response (e.g., a major response for function and a non-response for size would score as a major response overall). Subjects who were then classified as having a major response were then included in the major responder dataset.

Secondary study variables included muscle quality, total body weight, physical activity and quality of life.

Statistical Model

The sample size was determined by practical considerations and not based on statistical power calculations.

The sample size of 13 subjects in the efficacy analysis was selected to give an 80% power of rejecting a reference portion of muscle responders of 10% with an exact 5% one-sided test when the true proportion of muscle responders is at the clinically relevant value of 40%. The hypothesis that the true proportion of muscle responders was equal to or less than the reference portion would be rejected if 4 or more of the 13 subjects were muscle responders.

Results

Out of the 9 subjects who comprised the efficacy analysis population, 6 subjects (67%) achieved a major overall muscle response. Responders showed a high degree of consistency in degree of improvement between lower limbs (knee extension) and upper limbs (hand grip); and between left and right sides. Improvements in muscle strength were closely mirrored by increase in muscle size.

Among subjects who completed 8 weeks of therapy, the average increase in knee extension strength was 9% for the left leg and 8% for the right leg. The average increase

in quadriceps volume was 3% for the left leg and 1% for the right leg.

Safety assessments performed during the study showed that the combination of megestrol and formoterol had no clinically significant effects upon vital signs, ECG parameters, laboratory parameters or physical examination findings. The adverse event profile was similar to that seen historically with each drug alone.

The study demonstrated that the combination of megestrol and formoterol is well tolerated in patients with cancer cachexia and delivers clinically relevant improvements in muscle size and strength after eight weeks of treatment.

Date of report: 01 November 2012