The Christie
Research Division

Wilmslow Road
Manchester
M20 4BX

Mobile tel: 07894 464 384
Switchboard tel: 0161 446 3000
Email: amelie.harle@christie.nhs.uk
Web: www.christie.nhs.uk

12th May 2015

Ms Helen Penistone
Committee Co-ordinator
NRES Committee North West – Liverpool East
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Dear Ms Penistone

Title of Study: CALC – Aprepitant for the treatment of cough in lung cancer
REC REFERENCE Number: 13/NW/0084
Eudract number: 2013-000139-28

Please find attached the End of Trial report for the above mentioned CALC trial.

Please do not hesitate to contact me should you require any further information.

Yours sincerely

Dr Amélie Harle
NIHR Research Fellow

End of Trial Report to REC & MHRA (12th May 2015)

Study title:	A single arm double-blind placebo controlled cross-over trial of aprepitant for the treatment of cough in lung cancer: "CALC" Trial
EudraCT number:	2013-000139-28
REC reference:	13/NW/0084
Protocol number:	12_DOG07_146

Introduction

Cough in lung cancer is a significant unmet clinical need. It affects more than 65% of patients with advanced lung disease. It can be the result of metastatic spread to the lungs, specific complications of cancer or even due to treatment. To date, cough has received minimal attention amongst researchers. Yet, it can be distressing and lead to decreased quality of life (QoL). Whilst much research is focused on determining novel anti-cancer therapies, little research is carried out in the field of symptom control. Management options for cough in malignant disease are limited. While anticancer therapy such as surgery, chemotherapy and radiotherapy can improve a range of symptoms including cough, lung cancer often progresses or relapses following treatment, leading to a recurrence of symptoms. A recent Cochrane review assessing interventions, both pharmacological and non-pharmacological, for the management of cough in cancer showed the almost complete absence of any credible evidence for cancer patients. Neurotransmitters such as neurokinins are known to be important mediators of cough in the central nervous system of animal models. Therefore, centrally-acting neurokinin receptor antagonists, such as aprepitant, may prove to be effective treatments for cough in humans. Aprepitant is a highly selective NK1 receptor antagonist which readily crosses the blood-brain barrier. To date, no human studies have been conducted to explore the role of centrally acting neurokinin receptor antagonists for cough. There is therefore an urgent need to develop effective therapies for the management of cough in order to enhance the QoL of many lung cancer patients in the future.

Methods

Participants were randomised between aprepitant and placebo. Participants took a fixed dose-titration schedule of aprepitant, starting with 125mg on day 1 and then reducing the dose to 80mg on day 2 and day 3. Those participants receiving placebo received matched capsules on days 1, 2 and 3. On days 4-6 inclusive, both groups of participants stopped their treatment (wash-out period). Participants then crossed over to the alternative treatment (placebo or aprepitant) and received this treatment for 3 consecutive days (days 7-9 inclusive).On day 13 or 14, investigators contacted patients by telephone to ensure that there was no AE or SAE that required intervention and reporting. Participants completed a VAS and the Manchester Cough in Lung Cancer Scale (MCLCS) and underwent 24 hour ambulatory cough monitoring on days 0, 3 and 9. The GRCS was completed on days 3 and 9 only. Participants also completed the BRI and the EORTC QLQ C30+LC13. Participants also underwent blood sampling on Days 0, 3 and 9 for biomarker analysis.

Results

Between 7th October 2013 and 4th November 2014, 20 patients were recruited at The Christie NHS Foundation Trust. (Manchester, UK). There was high compliance with the study schedule and consequently little missing data, only one patient failed to complete the trial protocol due to a chest infection. The research population's mean age was 66years (SD 7.69). Nearly two thirds of the population, 12 (60%) patients, was female. The majority had a history of smoking; their median number of pack years was 37 (25th-75th IQ range 15-60). Most of the patients were of good performance status, with 4 patients (20%), 11 patients (55%), 5 patients (25%) of performance status 0, 1 and 2 respectively. The majority, 16 patients (80%), had NSCLC; 4 patients (20%) had SCLC. Half the patients had advanced lung cancer with 10 patients (50%) having stage IIIB or above NSCLC. No patients had extensive stage SCLC but 6 patients (30%) had early stage (≤IIIA) NSCLC and 4 patients (20%) had early stage SCLC. Most patients had had a cough for a prolonged period of time, with a median of 76 weeks with a wide range (25th-75th IQR 35-140). The median cough severity VAS score was over half the total possible score at 59mm (25th-75th IQR 37-66, score range 0-100 where higher scores represent worse cough severity. The median Manchester Cough in Lung Cancer Scale (MCLCS) score was about half the total score range at 25.5 (25th-75th IQR 20-31, range 1-50 where higher scores represent worse cough impact. Overall, the mean EORTC Lung Cancer 13 Item 31 score was 61.6 (SD 19.6) where higher scores indicate worse cough severity on a scale of 0-100. Objective cough monitoring was conducted in 20 patients at baseline (day 0) but one patient was excluded since they commenced treatment at baseline rather than on day 1. Of these, no recordings failed. The baseline geometric mean cough frequency over 24 hours was 13.3 coughs/hour with a 95%CI of 8.2-21.6 (n=19). The daytime (defined as hours patient awake) cough frequency was 15.9 coughs/hour with a 95% CI of 10.1-28.3 (n=19). The night-time (defined as hours patient asleep) the median cough frequency was 5.6 coughs/hour with a 25th-75th IQR of 1.9-10.7 with a total range of 0-17.45 (n=19).

Within the trial population, a subset of patients responded to treatment with aprepitant and showed improvement in both their subjective and objective cough scores. However, other patients showed no improvement in their cough counts or subjective measures. The baseline day-time cough frequency did not predict or influence the response to treatment (p=0.17). Since the CTCAE v4.0 and EORTC QLQ LC13 scales are 3 and 4-point scales respectively, there was little change in the overall score for individual patients during treatment with placebo and aprepitant. Most patients had stable cough severity CTCAE scores throughout the trial. Of the 19 patients, physicians reported an improvement from baseline of one point in 4 (20%) patients receiving aprepitant compared to 2 (10%) patients receiving placebo. There was no worsening of cough severity on treatment (aprepitant or placebo) compared to baseline using this scale during the trial. Similarly, the EORTC QLQ LC13 cough item only varied by one point for individual patients. Overall, 8 (40%) patients reported an improvement from baseline of one point in cough severity on aprepitant compared to 5 (25%) patients reporting an improvement on placebo from baseline.

Conclusion

Overall, this study has shown that the NK1 pathway warrants further investigation in a larger scale trial in order to determine whether this might be an appropriate antitussive therapy target for future patients with lung cancer-related cough. This project was successful in achieving its goals and future publications to the New England Journal of Medicine are planned to be submitted.