Aprepitant For Cough in Lung Cancer: A Randomised Placebo-Controlled Trial and Mechanistic Insights

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AJRCCM Articles in Press. Published September 23, 2020 as 10.1164/rccm.202006-2359OC
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Author's contributions: Conception and design; clinical study AH, FB, JAS, pre-clinical experiments MGB and MAB; Data generation and analysis; clinical study AH, RD, KH, PR, AM, JY, FB, JAS, pre-clinical experiments RR, MGB and MAB; Drafting of the paper; AH, JAS, FB and MGB; all authors reviewed the manuscript and approved the final draft.

Funding: National Institute of Health Research, North West Lung Charity, Nerre Pharmaceuticals, BBSRC Studentship for RR, Wellcome Investigator Award (207504/B/17/Z).

Running Head: Aprepitant for Lung Cancer Cough

Descriptor No: 9.15 Cough: Clinical

Word Count: 3175 words

Clinical Trial Registration: ISRCTN16200035 https://www.isrctn.com and EU Clinical Trials Register (EudraCT Number 2013-000139-28).

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At a Glance

What is the current scientific knowledge on this subject?

Neurokinin 1 (NK-1) antagonists are established therapies for the treatment of chemotherapy-induced nausea and vomiting, acting in the central nervous system, however this receptor and it's natural ligand, substance P have also been implicated in the cough reflex. Effective treatments for cough associated with lung cancer are a significant unmet need.

What does this study add to the field?

An NK-1 antagonist (aprepitant) significantly reduced cough frequency in a randomised controlled trial of lung cancer patients and also inhibited substance P activation of vagal tissue . Substance P activation of NK-1 receptors may be an important mechanism driving cough in lung cancer and NK-1 antagonists show promise as anti-tussive therapies.

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ABSTRACT

Rationale: Effective cough treatments are a significant unmet need in lung cancer patients. Aprepitant is a licensed treatment for nausea and vomiting, which blocks substance P activation of Neurokinin 1 (NK-1) receptors, a mechanism also implicated in cough.

Objective: To assess aprepitant in lung cancer patients with cough and evaluate mechanisms in vagal nerve tissue.

Methods: Randomised double-blind crossover trial of lung cancer patients with bothersome cough. They received three days of aprepitant or matched placebo; following a three day wash out, patients crossed to the alternative treatment. The primary endpoint was awake cough frequency measured at screening and day 3 of each treatment; secondary endpoints included patient-reported outcomes. In vitro, the depolarization of isolated guinea pig and human vagus nerve sections in grease gap recording chambers, indicative of sensory nerve activation, was measured to evaluate mechanism.

Measurements and Main Results: Twenty lung cancer patients enrolled, mean age 66years (±7.7), 60% female, 80% non-small cell cancer, 50% advanced stage and 55% WHO performance status 1. Cough frequency improved with aprepitant, reducing by 22.2%(95%CI 2.8-37.7%) over placebo whilst awake (p=0.03), 30.3%(95%CI 12.7-44.3) over 24hours (p=0.002) and 59.8%(95%CI 15.1-86.0) during sleep (p=0.081). Patient-reported outcomes all significantly improved. Substance P depolarised both guinea pig and human vagus nerve. Aprepitant significantly inhibited substance P induced depolarisation by 78% in guinea pig (p=0.0145) and 94% in human vagus (p=0.0145).

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Discussion: Substance P activation of NK-1 receptors appears to be an important mechanism driving cough in lung cancer, and NK-1 antagonists show promise as anti-tussive therapies.

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INTRODUCTION

Lung cancer is the leading cause of death from cancer in the UK, accounting for 35,300 deaths annually 2015-17(1). Until recently the morbidity associated with chronic coughing in lung cancer patients was underestimated, and hence the treatment of cough in such patients remains an important unmet need. In an unselected UK lung cancer population attending oncology outpatient clinics, over half of patients reported cough and two-thirds of these felt it was severe enough to warrant treatment(2). Chronic coughing is known to impact on physical, psychological and social aspects of daily living, but in lung cancer cough also contributes to pain, fatigue, dyspnoea, social isolation and anxiety(3). Effective cough therapies are lacking, in part due to our limited understanding of the underlying pathophysiology, but also due to the lack of well-designed trials incorporating validated endpoints(4). Moreover, it is often assumed that symptoms will improve with anti-cancer therapy, yet despite the development of more effective treatments, cough often persists(5).

Cough is mediated by vagal afferent nerve fibres innervating the larynx and airways, synapsing in the nucleus tractus solitarius (nTS) and paratrigeminal nucleus of the brainstem(6). Pre-clinical experiments show vagal airway C fibres are capable of manufacturing substance P (SP), a neuropeptide active at the neurokinin 1 receptor, NK-1. Although SP is primarily a neurotransmitter, it is also produced by inflammatory cells including mast cells, macrophages, eosinophils, lymphocytes, and dendritic cells(7). In the central nervous system, the nTS is enriched with SP immuno-reactive nerve terminals and microinjection of SP into this region enhances cough responses, via the NK-1 receptor(8). Furthermore, exposures such as cigarette smoke increase SP synthesis in vagal airway fibres enhancing synaptic transmission and cough responses, both blocked by NK-1 receptor

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antagonism(9). In animal models, NK-1 antagonists inhibit cough responses to inhaled irritant agents in five different species(10).

Although, two previous clinical trials failed to demonstrate antitussive effects of NK-1 antagonism (11, 12), progress has been made since in cough assessment tools, including validated quality of life questionnaires and objective cough monitoring systems. Given the limitations of previous study endpoints, and the poor CNS penetrance of some clinically tested compounds, the potential for a centrally acting NK-1 antagonist to be an effective anti-tussive treatment has never been ruled out. This study therefore aimed to provide proof of concept that NK-1 antagonism improves cough associated with lung cancer and to offer some insights into the possible mechanism of action. To do this we assessed the anti-tussive effect of aprepitant, a potent, centrally active NK-1 receptor antagonist, developed and licensed to treat chemotherapy-induced nausea and vomiting. We conducted a placebo-controlled study measuring objective cough frequency and validated patient-reported outcome measures in patients with troublesome cough associated with lung cancer. In addition, we assessed a possible peripheral mechanism of action by performing *in vitro* mechanistic studies to assess the activity of Aprepitant on vagal nerve depolarisation. Some of the results of these studies have been previously reported in the form of abstracts (13, 14)

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METHODS

CLINICAL STUDY

Study Design

We performed a randomised double-blind placebo-controlled crossover trial in patients with cough associated with lung cancer attending oncology outpatient clinics at The Christie NHS Foundation Trust, Manchester, UK, Figure 1. Patients received a standard antiemetic course of aprepitant therapy (three days duration; 125mg od on day1 and 80mg od on days two and three) or matched placebos; for randomization details see online supplement. After a three-day washout period, patients crossed over to the alternative treatment (placebo or aprepitant) for a further three days treatment. Cough was assessed at screening and on day three of each treatment using an ambulatory cough monitoring system and patient-reported outcomes including a cough severity visual analogue scale (VAS), cough impact questionnaire (Manchester Cough in Lung Cancer Scale, MCLCS(15)), and global rating of change scale. A final follow-up evaluation was performed over the telephone at day 13/14

Patients

Adult patients with histologically confirmed non-small cell or small cell lung cancer and a bothersome cough (≥4 weeks duration) were enrolled. Patients with a World Health Organization performance status (PS) score of 0-2, willing and able to comply with the study protocol, were eligible. The main exclusion criteria were subjects due to commence anti-cancer therapy during the trial, those within 6 weeks of commencement of chemotherapy, within 8 weeks of starting a tyrosine kinase inhibitor and those receiving/within 12 weeks of completion of thoracic radiotherapy. Patients taking other treatments that may modulate

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cough such as steroids, opiates, pregabalin or gabapentin were included, as long as the cough was still troublesome, they had been on treatment for at least 4 weeks, and the dose remained stable for the duration of the study. Patients on antibiotics were excluded from the trial, as were those reporting a respiratory tract infection within 4 weeks of enrolment. Ethical approval for the study was obtained from the local Research Ethics Committee (ref: 13/NW/0084) and all patients provided written informed consent.

Procedures

Data on patient demographics, cancer characteristics, anticancer treatment and co-morbidities were collected at screening. Subjects underwent efficacy assessments at screening and during the last 24 hours of each three-day treatment period. Safety was assessed through monitoring of adverse events, physical examinations and vital signs. Concomitant medications were monitored throughout the study.

The primary endpoint was awake objective cough frequency collected using a cough monitoring device (VitaloJAK™, Vitalograph Ltd, Buckinghamshire, UK); sleep and 24-hour cough frequency were also determined(16). Secondary endpoints included changes in a 100mm cough severity VAS, cough specific quality of life (MCLCS)(15) and 15-point global rating of change scales for both cough severity and cough frequency at the end of each treatment period. Subjects also completed the European Organization for the Research and Treatment of Cancer Quality of Life Core Questionnaire and Lung Cancer Module (EORTC QLQC30+LC13). Researchers rated the patients' cough using the Common Terminology Criteria for Adverse Events (CTCAE version 4). For additional details of procedures, see online supplement.

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Statistical Analyses

The effect of treatment (aprepitant versus placebo) on awake cough frequency was assessed using General Estimating Equations (GEE) modelling of log transformed data (SPSS version 22, IBM Corp, NY). The model was adjusted for the effect of baseline cough frequency and also assessed any influence of treatment sequence and period. Similar models were used to assess the effect of treatment on 24h cough frequency, sleep cough frequency, cough severity VAS, MCLCS, global rating of change scales, CTCAE score and EORTC item 31 responses.

The sample size calculation used data from refractory chronic cough patients(17). Based on a paired t-test, 18 participants were needed to detect a difference in cough frequency of 30% between aprepitant and placebo, at 5% significance and 90% power, assuming the change in 24h cough frequency was normally distributed with a standard deviation of 36.5%. Data in participants with refractory chronic cough suggests that a 20-30% decrease in cough frequency from baseline is likely to be the minimal clinically important difference(18). Allowing for 10% attrition, the recruitment target was 20 patients to obtain complete data on 18.

PRE-CLINICAL STUDIES

Animals

Male guinea-pigs (Dunkin-Hartley, Harlan, UK) weighing 300-500g were housed in temperature-controlled (21°C) facilities for at least 1 week prior to any procedures. Experiments were performed in accordance with the U.K. Home Office guidelines for animal

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welfare based on the Animals (Scientific Procedures) Act of 1986 and the ARRIVE guidelines(19).

Human tissue

Vagal nerve tissue which is surplus to donor requirements, was acquired and consent for use obtained by the International Institute for the Advancement of Medicine (Edison, New Jersey, US). Approvals for use in scientific research and ethics were obtained from the Royal Brompton & Harefield Trust (Ref: 09/H0708/72).

Collection of isolated vagus nerve

Guinea-pigs were sacrificed by overdose of pentobarbitone (200mg/kg i.p.); vagus nerve trunks were dissected as described previously(20). Human vagus nerve trunks were placed into Krebs-Heinseleit (KH) solution, which was gassed with 95% O2/5% CO2, at room temperature, until use.

Recording of isolated vagus nerve depolarisation

Segments (approx. 15mm) of guinea-pig or human vagus nerve were mounted in a 'grease-gap' recording system(21). The nerve segments were perfused constantly with KH solution (at 37°C bubbled with 95% O2/5% CO2) and following each stimulus, depolarisation was recorded on a Lectromed 2 (Digitimer) chart recorder with DAM50 differential amplifier (WPI instruments, UK).

Stock solutions of SP (Sigma, UK) were prepared using 0.1% BSA in dH20, while stock solutions of aprepitant (Cayman Chemical, USA) were prepared in neat DMSO. Stock solutions were aliquoted and kept at -20^{o}C until use on the day of the experiment, where

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they were diluted to working concentrations with modified Krebs-Henseliet solution (Krebs, in mM: NaCl 118; KCl 5.9; MgSO4 1.2; NaH2PO4 1.2; CaCl2 2.5; glucose 6.6; NaHCO3 25.5).

Two repeatable baseline responses to SP (1μM, concentration chosen from response curves) were first obtained before pre-treatment with the NK-1 antagonist aprepitant (10μM) for 10 minutes prior to a two-minute application of the SP in the presence of the aprepitant. After a ten-minute wash out, a recovery response to SP was then obtained to confirm nerve viability at the end of the experiment. If a recovery response could not be obtained, the data was disregarded.

RESULTS

Patient Characteristics

Twenty patients were recruited between October 2013 and November 2014. Baseline demographics and clinical characteristics are shown in Table 1 and patient study flow in Figure 2. One patient was withdrawn after the first treatment due to a respiratory tract infection and a second after starting the treatment at screening in error. Otherwise, there was very high compliance with the study schedule and no missing data, as seen in Table 2.

Efficacy Assessments

Following three days of aprepitant treatment, awake cough frequency was significantly improved compared with placebo treatment, a reduction of 22.2% (95%CI 2.8-37.7%) over placebo (p=0.03), see Table 2 and Figure 3A. Of note, the reduction in awake cough frequency with placebo treatment in this study was extremely small (0.0%, 95%CI 0.4% to -1.8%). There was no significant effect of treatment sequence or period and no significant interaction between baseline awake cough frequency and the efficacy of aprepitant,

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suggesting the treatment effect was independent of screening cough frequency. Age and gender also had no significant influence on efficacy. Of note, an intention to treat analysis (including the patient who took the study treatment at screening in error) produced almost identical results with a reduction of 22.7% in awake cough frequency, p=0.03. Cough frequency also improved over the whole 24h recording period [mean reduction 30.3% (95%CI 12.7-44.3), p=0.002] and during sleep [59.8% (15.1-86.0), p=0.081], however cough frequency during sleep is highly variable over time and therefore the effects did not quite reach statistical significance, Figures 3B and 3C.

Importantly, all patient-reported cough measures also significantly improved. The mean cough severity VAS score improved by 9.5mm (95%CI 3.5-15.4) over placebo treatment (p=0.002). Improvements were also seen in MCLCS cough specific quality of life score, EORTC Quality of Life Core Questionnaire and Lung Cancer Module (Table 2) and in the global rating of change scales for both cough frequency (p=0.001) and cough severity (p=0.028). Researchers also rated the patients' cough with the CTCAE as improved with aprepitant compared with placebo (Table 2).

Safety

Aprepitant was well tolerated with only mild adverse events reported. There were no serious adverse events and no grade 3 or 4 toxicities (severe/life-threatening), however there was a greater number of adverse events on aprepitant compared with placebo (Table 3).

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PRE-CLINICAL STUDIES

Isolated vagus nerve responses to Substance P

In vitro, substance P depolarized the guinea pig vagus nerve in a concentration dependent manner, Figure 4A. SP (1μM) was selected for further antagonist studies. In the isolated guinea pig vagus, pre-treatment with aprepitant (10μM; 0.1% DMSO) significantly inhibited responses to SP (1μM) from 0.083 mV ±0.007 to 0.0180 mV ±0.008, a reduction of 78%, (p=0.003, n=5), Figure 4B. Pre-treatment with vehicle (0.1% DMSO) had no effect on SP (1μM) responses (p=0.882, n=4). These results were mirrored in human tissue (n=3 female, 67-73yrs) where aprepitant (10μM; 0.1% DMSO) significantly inhibited responses to SP (1μM) from 0.087 mV ±0.013 to 0.003 mV ±0.003, a reduction of 97%. (p=0.0145; n=3), Figure 4C.

DISCUSSION

To the best of our knowledge, this is the first placebo-controlled study to objectively demonstrate the anti-tussive efficacy of a neurokinin-1 antagonist in humans, and also the first trial in patients with lung cancer to employ acoustic cough monitoring. The improvements in cough frequency, reductions over placebo of 22% during awaking hours and 30% over the whole 24h period, were sufficient to be appreciated by study participants, who recorded significant improvements on all patient-reported outcomes, striking given the very short (three day) duration of treatment. Furthermore, our pre-clinical data provides mechanistic insights, suggesting inhibition of peripheral vagal nerves may contribute to the influence of aprepitant on coughing, in addition to an effect in the central nervous system that might be predicted based upon the anti-emetic mode of action.

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The control of cancer symptoms is a key component of palliative care, which when delivered early to patients with metastatic, incurable NSCLC has been shown to not only improve quality of life and mood, but also prolong survival(22). Yet effective therapies to address the main symptom cluster in lung cancer, breathlessness, cough and fatigue, are lacking. Indeed, efficacious agents for cough in any clinical condition are needed. Recent progress in the development of treatments for refractory chronic cough has suggested that therapies specifically targeting neuronal function, via P2X3 antagonism, may be effective(23-25). This study provides the first objective evidence that a similar approach may also be valuable in cough associated with lung cancer. However it should not be assumed that treatments targeting specific neuronal mechanisms will implicitly be effective for cough across a range of respiratory diseases. Recent evidence suggests changes in airway nerve function are likely to be disease-specific and therefore treatments may need to be tailored to particular neuro-phenotypes in respiratory disorders(26). Indeed, two recent phase 2b studies of other centrally acting NK-1 antagonists (serlopitant and orvepitant) in patients with refractory chronic cough rather than lung cancer both failed to achieve their primary endpoints(27, 28).

Whilst the improvements achieved with aprepitant could be considered modest compared with those seen with P2X3 antagonism in refractory cough (37-75% reductions over placebo over treatment periods of up to 12 weeks), the duration of treatment in this study was much shorter by comparison. Nonetheless, the improvement in the cough severity VAS after 3 days aprepitant treatment reported in this study approached that seen with 10 weeks of gabapentin treatment (12mm over placebo) in refractory chronic cough(29) and the reduction in the MCLCS is comparable to that reported in a 12-week feasibility study of a

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non-pharmacological intervention to address a respiratory distress symptom cluster in lung cancer(30). Further work is needed to evaluate whether NK-1 antagonism will deliver anti-tussive benefits with longer treatment durations but the involvement of substance P and NK-1 receptors in neuroplastic changes at synapses in the brainstem would suggest greater benefits might be expected from long term therapy. Consistent with this notion, an un-blinded trial, inspired by this study, recently randomised 128 advanced lung cancer patients to receive aprepitant or standard antitussive therapy for 7 days(31). Although objective cough monitoring was not used, and the study was not placebo-controlled, significant improvements in cough severity VAS and MCLCS were found at day 9 over standard antitussive care, and the absolute changes were increased compared with those seen in this study.

The participants in this study were typical of a lung cancer outpatient population. The greater proportion of female patients may be a consequence of selecting those with troublesome cough. Women are over-represented in specialist clinics treating chronic cough(32) and even in health women exhibit heightened cough reflex responses compared with men(33). It is notable that at enrolment to this study almost half of patients were taking opioid treatments and the majority had completed anti-cancer therapy, yet all still suffered from bothersome coughing with cough frequencies comparable to patients presenting with chronic cough as their main complaint(34).

Aprepitant and Fosaprepitant, the intravenously administered prodrug of aprepitant, are currently the only licensed NK-1 antagonists in the UK, with Rolapitant also available in the United States. Used in the prevention of chemotherapy-induced and postoperative nausea and vomiting, the anti-emetic effects of NK-1 antagonists are thought to occur in the

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brainstem, where they prevent activation of the area postrema and nucleus tractus solitarius by afferent vagal inputs from the gastro-intestinal tract and circulating emetic agents. Apart from their role in emesis, SP and the NK-1 receptor have been implicated in the regulation of a number of physiological and pathophysiological processes including pain, inflammation, anxiety/depression and itch, and thus newer NK-1 antagonists have been explored as anti-depressants and anti-pruritics. NK-1 receptors are thought to play an important role in both inducing and maintaining pruritus through both peripheral inflammatory mechanisms operating in the skin and processes in the central nervous system. In the skin, substance P released by activation of a sub-group of C fibres plays a major role in the induction of 'neurogenic inflammation', producing vasodilation and inflammatory cell recruitment. In rodents, a similar effect can be observed in the airways, with tachykinin release additionally producing bronchoconstriction and mucus hypersecretion. The reporting of airway neurogenic inflammation in rodent models previously led to considerable efforts to develop a variety of NK antagonists as novel asthma therapies, however disappointing results in phase II clinical trials questioned the relevance of such mechanisms in asthma and in humans(35). Whilst it is impossible to determine from our studies whether the main anti-tussive effects of aprepitant are located in the airways or central nervous system, our study does provide evidence of a possible inhibitory effect on peripheral nerves contributing to the mode of action of aprepitant. However, rather than C-fibres releasing tachykinins such as SP to evoke neurogenic inflammation and cause cough, our studies suggest that SP activates airway C-fibre afferents to evoke cough.

This study has some limitations. The clinical study sample size was small, as this proof of concept study was only powered to assess the effect of aprepitant on objective cough

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frequency. This limits the conclusions about the general applicability of aprepitant for the treatment of cough in patients with lung cancer and also restricts the analysis of predictors of response. Nonetheless, we were able to demonstrate significant improvements in a range of cough measurements including patients reported outcomes, therefore suggesting the improvements in objective cough frequency observed were clinically meaningful. In addition, the dose level and duration where determined by the licensed doses optimised to treat nausea and vomiting, and therefore the relevance of these to anti-tussive effects needs further exploration with studies including a range of doses and longer duration.

In conclusion, these data suggest that the substance P/NK-1 pathway plays a significant role in cough associated with lung cancer. Larger trials are warranted to evaluate this effect further, especially over longer treatment durations to determine whether anti-tussive effects are sustained or even enhanced. Anti-tussive efficacy, together with the established effects on nausea and vomiting and potential benefits for mood(36) and sleep quality(37), make the NK-1 receptor an attractive target for development of treatment to palliate lung cancer symptoms.

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ACKNOWLEDGEMENTS

This trial was primarily funded by the National Institute of Health Research (UK): Doctoral Research Fellowship awarded to Dr A Harle (DRF-2010-03-55) but also by donations from the North West Lung Charity and an unrestricted grant from Nerre Pharmaceuticals. The Christie NHS Foundation Trust acted as sponsor for the study. The study also received support from the NIHR Manchester Clinical Research Facility (Wythenshawe and Christie sites). JAS and MGB are funded by a Wellcome Investigator Award (207504/B/17/Z); JAS, JY and FB are additionally funded by the Manchester Biomedical Research Centre and JAS is an NIHR Senior Investigator.

DECLARATION OF INTERESTS

The VitaloJAK algorithm has been licensed by Manchester University Foundation Trust (MFT) and the University of Manchester to Vitalograph Ltd and Vitalograph Ireland (Ltd). MFT receives royalties which may be shared with the clinical division in which JAS works. MGB and MAB are employees of AstraZeneca.

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FIGURE LEGENDS

Figure 1. Study design of double-blind, randomised, placebo-controlled cross-over trial assessing aprepitant for the treatment.

Figure 2. Consort diagram showing study patient flow through trial. Only one patient withdrew due to development of a respiratory tract infection.

Figure 3. Efficacy measures for aprepitant and placebo treatments. Note logarithmic scale on y axes for awake (A) and 24h (B) cough frequency data. VAS = visual analogue scale (100mm=worse cough severity), MCLCS = Manchester cough in lung cancer scale (50=worse cough impact), CTCAEv4.0=Common Terminology Criteria for Adverse Events version 4.0 (grade 3=worse cough severity).

Figure 4 Concentration dependent depolarisation of guinea pig vagus with substance P (A), blocked by Aprepitant (B), a reduction of 78%, (p=0.003, n=5). Substance P depolarisation of human vagus also blocked by Aprepitant a reduction of 97%. (p=0.0145; n=3), Figure 4C (C) Example tracings from vagus nerve preparations showing two control depolarisation responses prior to addition of Aprepitant (10μM) and then showing response to substance P (1μM) recovered after washout (D). Data are mean (±sem).

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TABLES

Table 1. Baseline clinical and demographic characteristics.

Characteristics (n=20)		**N (%)**
Gender	Female	12 (60%)
	Male	8 (40%)
Age (years)		66years (±6.74)
Performance Status (WHO)	0	4 (20)
	1	11 (55)
	2	5 (25)
Smoking History	Never	1 (5)
	Ex	14 (70)
	Current	5 (25)
Smoking History Median No Pack Years		37 pack years (IQR 20-47)
Median Duration of Cough		17.5 months (IQR 9.3-31.3)
Co-morbidities (self-reported)	GORD	9 (45%)
	Asthma	0 (0%)
	COPD	6 (30%)
	Other	13 (65%)
Reflux according to BRI score	No	13 (65%
	Yes	7 (35%)
Type of Cough	Dry	9 (45%)
	Productive	11 (55%)
Concurrent Medications	Opiates	9 (45%)
	Proton Pump Inhibitors	10 (50%)
	ACE inhibitor	1 (5%)
	Steroids	3 (15%)
	Other (anticholinergics/salbutamol)	4 (20%)
Histology	NSCLC	16 (80)
	SCLC	4 (20)
NSCLC Histological Sub-type	Squamous	7 (44)
	Adenocarcinoma	5 (32)
	Large	1 (6)
	Mixed	1(6)
	Not otherwise specified	1(6)
	Bronchoalveolar	1 (6)
Stage*	ES SCLC	0 (0)
	LS SCLC	4 (20)
	IIIA NSCLC	6 (30)
	IIIB NSCLC	4 (20)

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	IV NSCLC	6 (30)
Tumour Location	Central	13 (65)
	Peripheral	7 (35)
Anticancer Therapy	On treatment	4 (20)
	Off treatment	16 (80)
Prior Anticancer Therapy	Chemotherapy	12 (60)
	Tyrosine Kinase Inhibitor	3 (15)
	Radiotherapy (thoracic)	12 60)
	Radiotherapy (brain)	3 (15)
	Radiotherapy (bones)	1 (5)
	Thoracic Surgery	0 (0)

GORD=Gastro-oesophageal reflux disease, COPD=Chronic Obstructive Pulmonary Disease, BRI=Brief Reflux Inventory, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer, LS=limited stage, ES=extensive stage, *cancer staged according to 7th Edition of TNM in Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2009

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Table 2. Efficacy endpoint data comparing screening to aprepitant and placebo.

	Screening	Aprepitant	Placebo	Placebo-adjusted effect of Aprepitant	p
Awake Cough Frequency					
geometric mean (95%CI)	16.3c/h (9.7-27.1)	12.1c/h (7.9-18.4)	16.1c/h (11.3-23.0)	-22.2% (-37.7,-2.8)	**0.026**
patients in analysis	19	18	19		
Sleep Cough Frequency*					
median (IQR)	4.6/h (1.9-10.0)	2.2c/h (0.5-5.4)	5.3c/h (1.8-13.0)	-59.8% (-86.0,15.1)	0.081
patients in analysis	19	18	19		
24h Cough Frequency*					
geometric mean (95%CI)	12.6c/h (7.8-20.4)	9.1c/h (6.0-13.9)	13.4c/h (9.6-18.7)	-30.3% (-44.3,-12.7)	**0.002**
patients in analysis	19	18	19		
Cough Severity VAS					
mean score (95%CI)	54.5mm (45.3-63.7)	39.6mm (32.3-46.8)	49.6mm (43.6-55.7)	-9.5mm (-15.4,-3.5)	**0.002**
patients in analysis	19	18	19		
Cough Impact MCLCS					
mean score (95%CI)	24.8 (22.1-27.5)	19.1 (17.1-21.1)	21.3 (19.6-23.0)	-2.0 (-3.2, -0.9)	**0.001**
Patients in analysis	19	18	19		
Item 31 EORTC QLQ-C30+LC13					
mean score (95%CI)	2.8 (2.6-3.1)	2.4 (2.1-2.6)	2.6 (2.3-2.8)	0.2 (0.0-0.4)	**0.016**
patients in analysis	19	18	19		
CTCAE v4.0					
mean score (95%CI)	2.0 (1.7-2.3)	1.7 (1.4-1.9)	1.9 (1.7-2.1)	0.2 (0.0-0.4)	**0.019**
Patients in analysis	19	18	19		
Global Rating of Change Scales					
Cough Frequency mean score (95%CI)	n/a	2.4 (1.4-2.3)	0.3 (-0.9 to 1.5)	2.1 (0.8- 3.3)	**0.001**
Cough Severity mean score (95%CI)	n/a	1.6 (0.4-2.8)	-0.8 (-1.2 to 1.0)	1.7 (0.2-3.2)	**0.028**
Patients in analysis	n/a	18	19		

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Table 3. Adverse events reported during the trial. All were Grade 1 and there were no serious adverse events; only 3 were thought to possibly relate to aprepitant.

Adverse Events	**Placebo** n=19	**Aprepitant** n=19
Constipation	0 (0%)	1 (5.5%)
Vomiting	1 (5.2%)	0 (0%)
Fatigue	0 (0%)	2 (11%)
Vertigo	1 (5.2%)	2 (11.0%)
Headaches	1 (5.2%)	0 (0%)
Dyspnoea	0 (0%)	1 (5.5%)
Gastro-Oesophageal Reflux Disease	1 (5.2%)	0 (0%)
Chest Infection	0 (0%)	1 (5.5%)
Pruritus Vagina	0 (0%)	1 (5.5%)
Conjunctivitis	1 (5.2%)	0 (0%)
Diarrhoea	0 (0%)	1 (5.5%)
Malaise	0 (0%)	1 (5.5%)

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FIGURES

Figure 1.

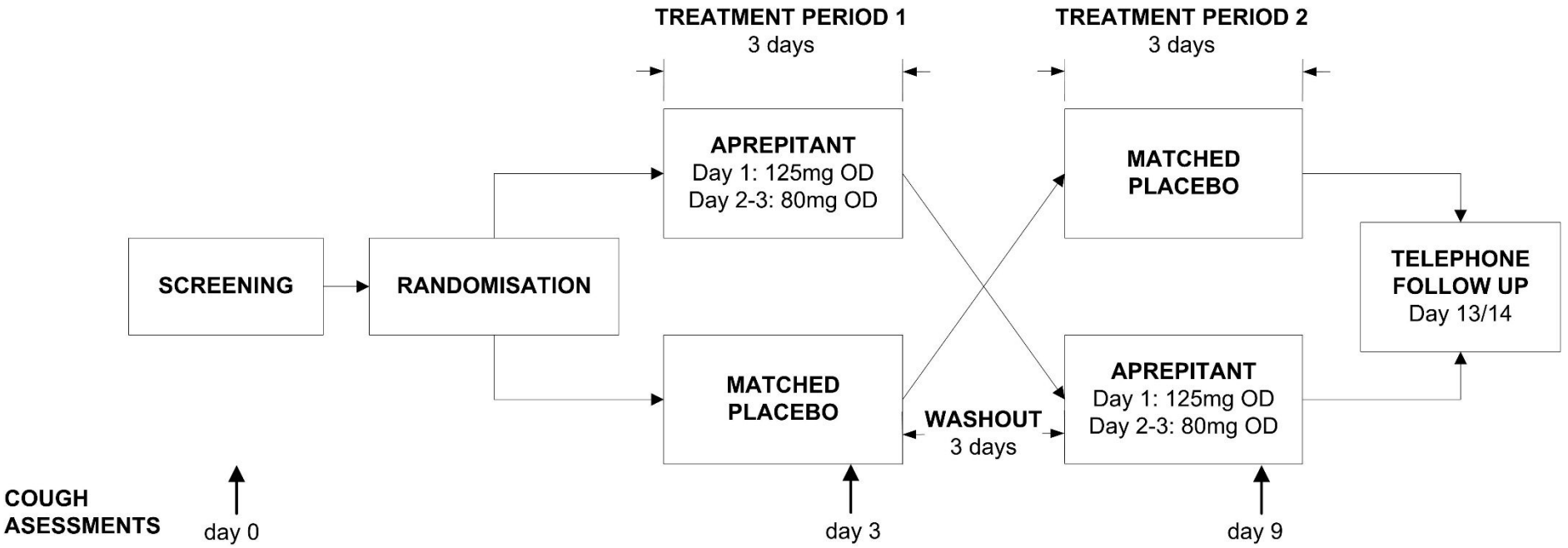

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Figure 2.

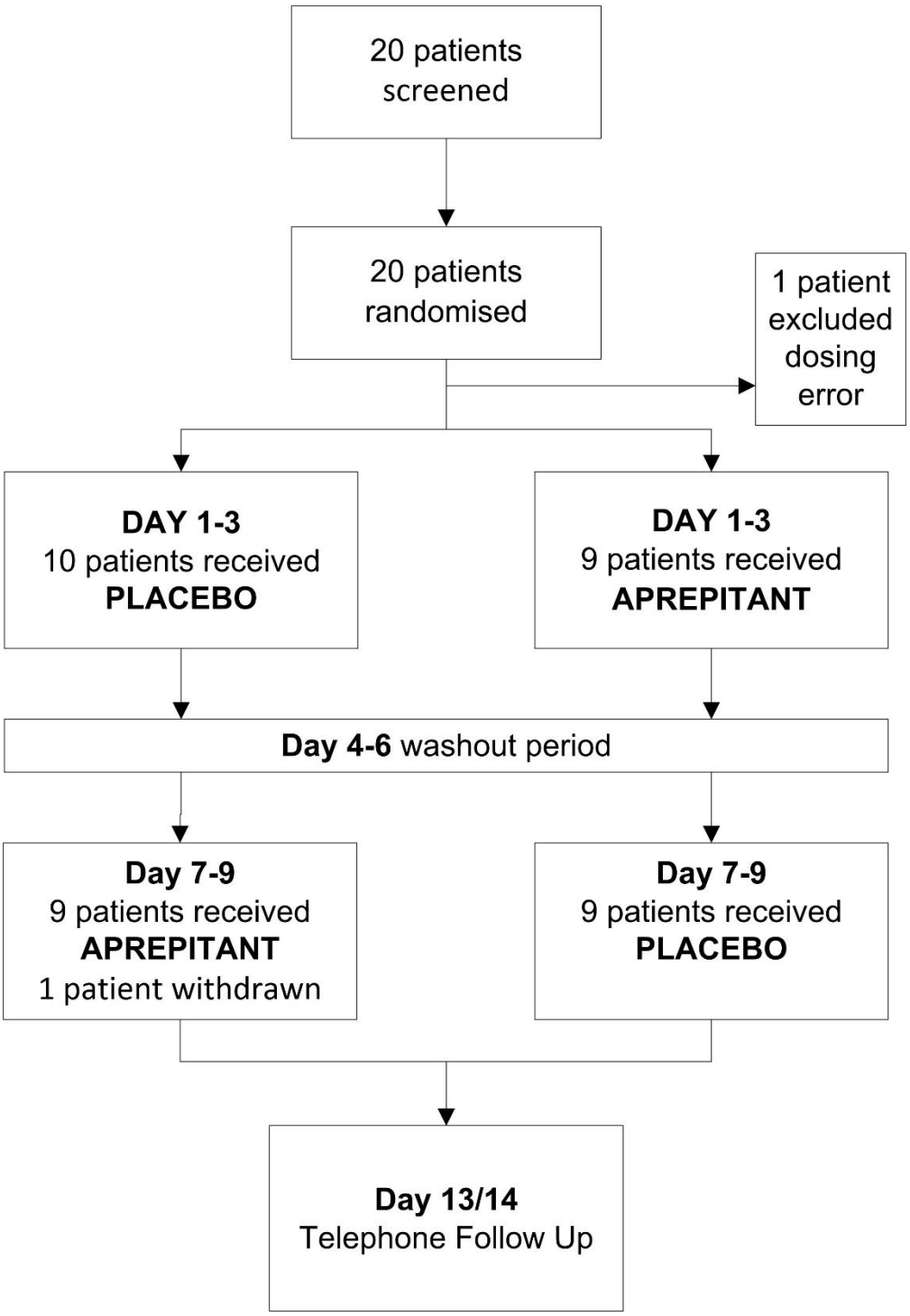

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Figure 3.

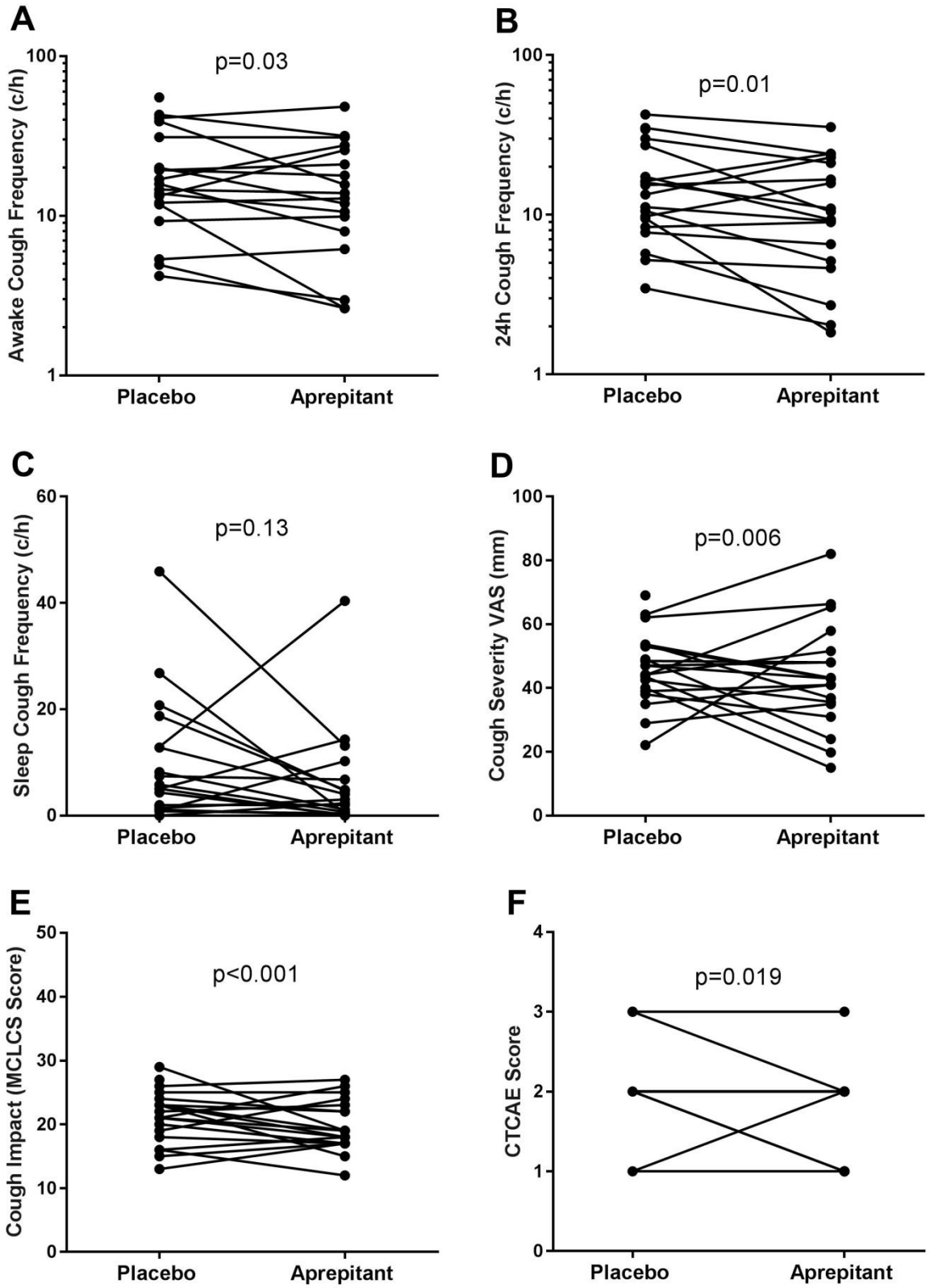

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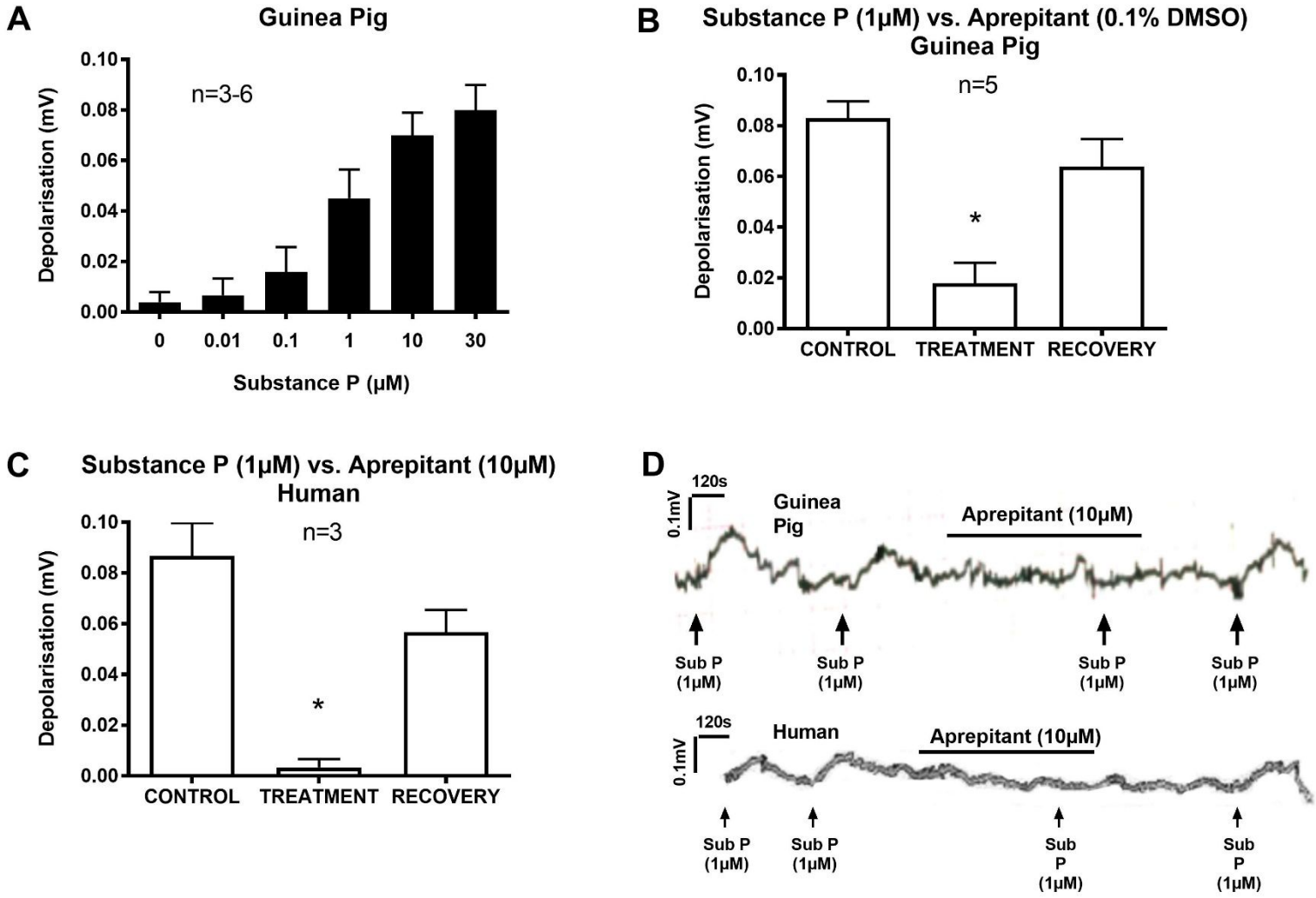
Figure 4.



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