Theobromine for the treatment of persistent cough: a randomised, multicentre, double-blind, placebo-controlled clinical trial

Alyn H. Morice[1], Lorcan McGarvey[2], Ian D. Pavord[3,4], Bernard Higgins[5], Kian Fan Chung[6], Surinder S. Birring[7]

[1]Hull York Medical School, Castle Hill Hospital, Hull, UK; [2]Centre for Experimental Medicine, Queen's University Belfast, Belfast, Northern Ireland; [3]Nuffield Department of Medicine, University of Oxford, Oxford, UK; [4]University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK; [5]Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle, UK; [6]National Heart and Lung Institute, Imperial College London, and Biomedical Research Unit, Royal Brompton & Harefield NHS Trust, London, UK; [7]Division of Asthma, Allergy and Lung Biology, King's College London, London, UK

Contributions: (I) Conception and design: AH Morice, L McGarvey, SS Birring; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: B Higgins, KF Chung, AH Morice, SS Birring, L McGarvey, ID Pavord; (V) Data analysis and interpretation: ID Pavord, KF Chung, AH Morice, L McGarvey; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Alyn H. Morice, MBBChir, MA, FRCP. Head of Cardiovascular and Respiratory Studies, Hull York Medical School, Castle Hill Hospital, Hull, HU16 5JQ, UK. Email: a.h.morice@hull.ac.uk.

Background: To investigate the effect of BC1036 on health-related quality of life (QOL) in subjects with persistent cough. The secondary objective was to investigate the effect of BC1036 on subjective cough severity.

Methods: This was a randomised, multicentre, double-blind, placebo-controlled, parallel-group study in 289 subjects with persistent cough. Subjects received BC1036 or placebo twice daily for 14 days. The primary endpoint comprised cough-related QOL assessed using the validated Leicester Cough Questionnaire (LCQ) at Day 14. Secondary endpoints comprised the LCQ scores at Day 7 and Day 28, cough severity VAS scores at each visit and pulmonary function tests.

Results: At baseline, mean total LCQ score in the BC1036 group was lower (i.e., worse QOL) than placebo (P<0.001), indicating significant between-group heterogeneity. Mean baseline-adjusted change in LCQ score at Day 14 was greater for BC1036 [mean (SD) 2.4±3.5] compared to placebo [mean (SD) score 2.2±3.0], but did not reach statistical significance (P=0.60). Mean cough severity VAS score decreased to a greater extent in the BC1036 group compared to placebo, but again the results were not statistically significant (–12.2±23.28 in BC1036 group and –11.0±21.34 in placebo group at Day 14, P=0.688). There was no significant change in pulmonary function measurements. The adverse event (AE) profile was similar in both groups.

Conclusions: This study showed that BC1036 was well tolerated and, although the primary endpoint did not achieve statistical significance, the magnitude of improvement was greater with BC1036 compared to placebo with respect to improving QOL and reducing cough severity.

Clinical trial registration: ClinicalTrials.gov: NCT01656668.

Keywords: Cocoa; controlled clinical trial; cough; quality of life (QOL); theobromine

Introduction

At any one time, 10% of the population have a persistent cough (1) and acute cough is the most common reason for new patient consultation in primary care. Sufferers consume 75 million doses of over-the-counter antitussive medication annually, totalling £98.7 million in the UK in 2014 (2,3). Codeine and dextromethorphan are the most commonly prescribed opioid-derived antitussives but their use is limited by unpredictable efficacy and unacceptable adverse events (AEs), such as somnolence, dizziness, nausea and constipation (4-7).

Theobromine is a methylxanthine alkaloid derivative that is predominant in cocoa (8,9). It has a long history of clinical use and has been suggested as a promising therapy for the treatment of persistent cough (4,10-12). BC1036 is a non-opioid, non-narcotic, theobromine treatment and its main mechanisms of action are inhibition of phosphodiesterases and blockade of adenosine receptors. Theobromine has been shown to inhibit the inappropriate firing of the vagus nerve, which is a key feature of persistent cough. This peripheral mechanism of action differentiates theobromine from codeine and other centrally acting agents, and lessens its lower central nervous system AEs. Theobromine has been approved since 2009 in Korea for persistent cough under the name AnyCough™ (developed by Ahn-Gook Pharmaceuticals, Seoul, South Korea). This study was carried out to assess the effectiveness of BC1036 for persistent cough in a randomised, controlled clinical trial setting. The primary objective was to investigate the effect of BC1036 on quality of life (QOL) in subjects with persistent cough. Secondary objectives were to investigate the effect of BC1036 on cough severity and objective cough reflex sensitivity.

Methods

Study design

This was a Phase III, randomised, multicentre, double-blind, placebo-controlled, parallel-group study conducted in 13 UK cough clinics and primary and secondary care centres between 13 July 2012 and 6 August 2013.

Subjects

Main inclusion criteria comprised males or females aged 18–75 years with a confirmed diagnosis of persistent cough. This was defined as a chronic cough lasting ≥8 weeks at baseline or a sub-acute cough lasting ≥3 weeks at baseline. Subjects were required to have a Leicester Cough Questionnaire (LCQ)[2] score of ≤17 at baseline and forced expiratory volume in 1 second (FEV_1) ≥70% of predicted normal at screening. Key exclusion criteria were an uncontrolled intercurrent illness, treatment with systemic oral steroids, theophylline or theophylline-like agents, or opiates or opioids within 7 days prior to randomization, significant sputum production on any 3 days in the screening period, or current smokers or past smokers who had a smoking history of >20 pack years. In addition, patients were excluded if any of the following applied:

- ❖ Any pulmonary abnormality on chest X-ray or computed tomography scan performed in the 12 months prior to enrolment indicative of chronic obstructive pulmonary disorder, bronchiectasis etc.;
- ❖ Subjects diagnosed with asthma who had suffered an exacerbation requiring hospitalisation within 4 weeks prior to screening;
- ❖ Any pulmonary co-morbidity such as chronic obstructive pulmonary disorder, recurrent lower respiratory tract infections (≥2 within 12 months of screening) and bronchiectasis where cough suppression could have led to sputum retention and infection;
- ❖ Pregnant or lactating females.

With respect to all current stable regimens of over-the-counter cough and cold remedies including antihistamines and decongestants, no regimen adjustments and new treatments could be initiated between Visit 1 and Visit 5.

Randomization

Eligible subjects were randomised to receive either BC1036 or placebo in a 1:1 ratio using RANCODE (version 3.6).

Study medication

Subjects were randomised to one of the following treatments, which were blinded by using the same capsules:

- (I) BC1036 capsules: 300 mg of theobromine per capsule, taken orally twice daily (morning and evening), approximately 12 hours apart, for 14 consecutive days. The dose selected was based on the pre- and post-marketing experience of theobromine 300 mg capsules in Korea.
- (II) Matching placebo capsules, taken orally twice daily (morning and evening), approximately 12 hours apart, for 14 consecutive days.

Compliance was calculated as: (Actual number of capsules

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used/prescribed number of capsules to be taken) ×100. A calculated compliance of <90% or >110% was classified as a major deviation.

Study schedule

Subjects attended the clinic on up to six occasions for consent, screening, baseline, Day 7 (±1 day), Day 14 (±1 day), and a follow-up visit at Day 28 (±2 days). At each visit subjects completed the LCQ, which is a validated, self-reported 19-item questionnaire with a 7-point Likert response scale for each question. The LCQ assesses the impact of cough on QOL over the previous 14 days. In addition to the LCQ, a 100 mm cough visual analogue scale (VAS) was recorded at each visit, using a scale of 0= no cough to 100= worst cough ever. Vital signs (pulse rate, blood pressure and body temperature) and pulmonary function were also measured at each visit. Blood and urine samples were collected for safety clinical laboratory parameters at screening and Day 28, and electrocardiograms (ECGs) were recorded at screening and Day 14.

Efficacy endpoints

The primary endpoint comprised cough-related QOL, assessed using the LCQ, with baseline-adjusted total LCQ score at Day 14 being the primary endpoint. The lower the total score, the greater the impact of the cough on various aspects of daily life (2).

Secondary endpoints comprised the baseline-adjusted LCQ scores at Day 7 and Day 28, the cough VAS scores at each visit, and pulmonary function tests at each visit [FEV_1, forced vital capacity (FVC) and peak expiratory flow (PEF) measured using a calibrated spirometer].

Ethics and trial registration

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by National Research Ethics Services Committee North East-Sunderland (approval: 11/NE/0375). All adult participants provided written informed consent to participate in this study. The clinical trial was registered on ClinicalTrials.gov with the registration number of NCT01656668.

Sample size justification and statistical analyses

A mean difference between BC1036 and placebo baseline-adjusted total LCQ score of 1.3 (SD 3.2) was considered clinically significant (13). Based on this assumption, for a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05, a sample size of 129 subjects per group was required to obtain a power of at least 0.9 to detect a mean difference of 1.3. Assuming a drop-out rate of 10%, this yielded a total sample size of 144 subjects per treatment, i.e., 288 subjects in total.

The primary efficacy endpoint (cough-related QOL assessed using the LCQ) was analysed by means of an analysis of variance (ANOVA), including treatment and centre effects. Two-sided 95% confidence intervals (CIs) for the difference of baseline-adjusted means between treatment groups were calculated. Missing values for the LCQ score were substituted with the last observation carried forward (LOCF). For all other secondary variables, baseline-adjusted scores were analysed for Days 7, 21 and 28 using descriptive statistics.

All safety data obtained in this study were tabulated with descriptive statistics or counts and percentages depending on the variable.

Results

Subject demographics

Of the 347 subjects screened, 291 were randomised at 13 UK centres (*Figure 1*). Subjects had a mean age of 57 years (range, 19–78 years) and a mean body mass index (BMI) of 28.3±5.3 kg/m². Females outnumbered males by 2:1 (191 females, 98 males) and more females were randomised to BC1036 (71.6% female, 28.4% male) compared to placebo (60.8% female, 39.2% male). There were no statistically significant differences between the treatment groups at baseline with respect to age, gender, ethnic origin, weight, height, BMI, or smoking history (*Table 1*).

Exposure to treatment

The study drug or placebo was administered to 289 subjects. Mean compliance was 98.3% for BC1036 and 97.5% for placebo. The mean duration of treatment was 14 days in both groups (range 12–21 days in the BC1036 group and 7–28 days in the placebo group).

Efficacy

Leicester cough questionnaire
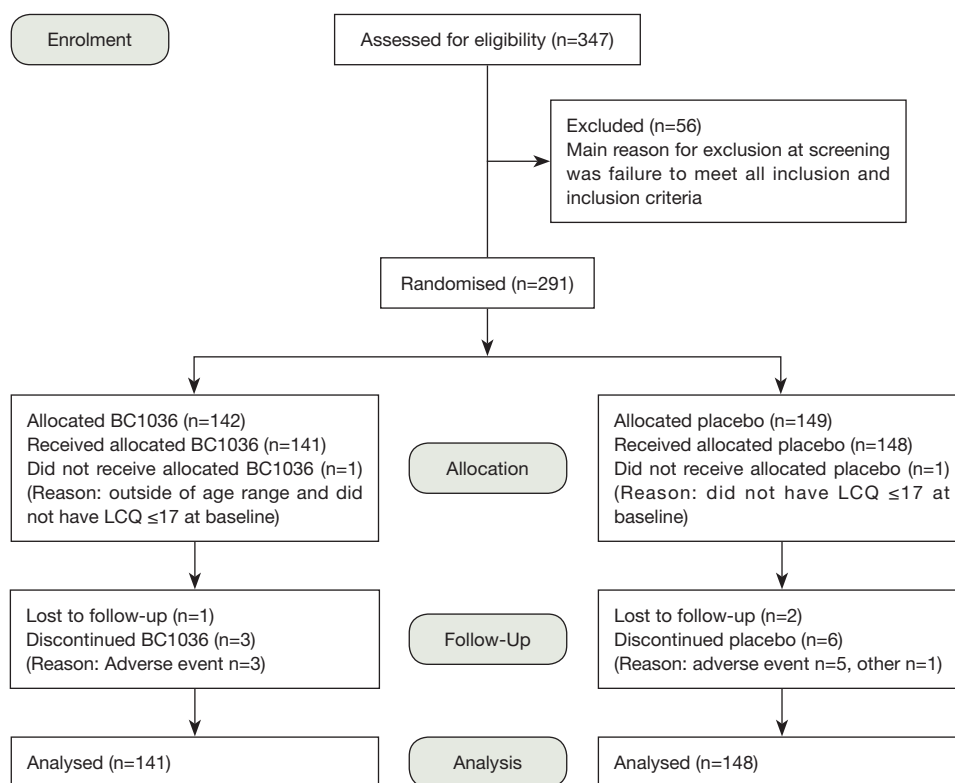The two groups were not matched for QOL at study entry.

Figure 1 CONSORT flow diagram. LCQ, Leicester Cough Questionnaire.

Mean total LCQ score at baseline in the BC1036 group was significantly lower than for placebo (i.e., had a worse QOL) (10.5±3.4 for BC1039 compared to 12.1±3.0 for placebo; P<0.001), indicating the treatment groups were not homogenous at baseline.

At all assessment points during treatment and follow-up (e.g., at days 7, 14 and 28), the mean baseline-adjusted score was greater for BC1036 compared to placebo, indicating a greater improvement in QOL compared to placebo treatment, but the difference between the groups did not reach statistical significance at any timepoint. At the primary endpoint of Day 14, the mean baseline-adjusted score LCQ was 2.4±3.5 for BC1036 and 2.2±3.0 for placebo (P=0.60; 95% CI: –0.98 to 0.48) (*Figure 2*). However, for both groups, mean scores were still in the moderately impaired range on the LCQ.

To further investigate the significant difference between the treatment groups at baseline, post-hoc analyses were conducted in a variety of subgroups of subjects to try to identify whether duration of cough, the LCQ score, or time between screening and the start of treatment, or a

combination of these factors, could explain this difference. A significant treatment effect was seen in the following 4 subgroups at Day 7, but in all 4 groups the baseline difference between treatment arms was still apparent:

❖ Subjects with an interval of >7 days between screening and Day 0 (7 days was used as the cut-off value because this was the washout period for prior medications before entry into the study);
❖ Subjects with an interval of >7 days between screening and Day 0 and baseline LCQ ≤14 (the LCQ of 14 was used since this is corresponds to a moderate cough);
❖ Subjects with an interval of >7 days between screening and Day 0 and cough ≥8 weeks;
❖ Subjects with an interval of >7 days between screening and Day 0 and cough ≥8 weeks and baseline LCQ ≤14.

At Day 14, no significant treatment effect was seen for any of the subgroups. Thus, no evidence was found in the post-hoc analyses explaining the significant baseline difference in LCQ between BC1036 and placebo.

Table 1 Demographic details (full analysis set)

Demographic	BC1036 (N=141)	Placebo (N=148)	Total (N=289)	P value
Age at signing informed consent				0.54*
Mean	56.6	57.6	57.1	
SD	12.49	11.87	12.16	
Gender				0.05‡
Male	40 (28.4)	58 (39.2)	98 (33.9)	
Female	101 (71.6)	90 (60.8)	191 (66.1)	
Ethnic origin				0.93‡
Caucasian	136 (96.5)	138 (93.2)	274 (94.8)	
Asian	0 (0.0)	5 (3.4)	5 (1.7)	
Black	4 (2.8)	4 (2.7)	8 (2.8)	
Other	1 (0.7)	1 (0.7)	2 (0.7)	
Height (cm)				
Mean	165.51	166.47	166.00	
SD	8.825	8.818	8.819	
Weight (kg)				
Mean	77.74	78.54	78.15	
SD	16.517	16.271	16.368	
BMI (kg/m^2)				0.90*
Mean	28.34	28.27	28.31	
SD	5.534	5.087	5.301	
Smoking status				0.36‡
Non-smoker	98 (69.5)	96 (64.9)	194 (67.1)	
Ex-smoker	43 (30.5)	52 (35.1)	95 (32.9)	
Current	0 (0.0)	0 (0.0)	0 (0.0)	
Number of pack years in ex-smokers				0.09*
Mean	9.9	7.7	8.7	
SD	6.39	5.63	6.06	
Cough present ≥8 weeks, n (%)	124 (87.9)	133 (89.9)	257 (88.9)	
Recruited at primary care sites, n (%)	72 (51.1)	73 (49.3)	145 (50.2)	

Number of pack-years not applicable for non-smokers. *, P value shows the difference between the BC1036 and placebo groups using analysis of variance (ANOVA) with factors treatment and centre without interaction; ‡, P value shows the difference between the BC1036 and placebo groups using Cochran-Mantel-Haenszel test stratified by centre. SD, standard deviation; BMI, body mass index.
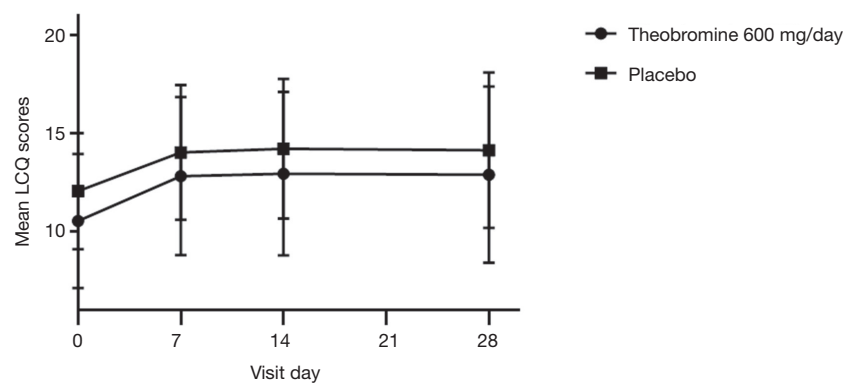
Figure 2 Effect of theobromine versus placebo on the change in mean (standard deviation) Leicester Cough Questionnaire (LCQ) scores.

Table 2 Baseline adjusted cough severity VAS: descriptive measures and results of ANOVA (full analysis set)

Baseline-adjusted VAS measurement result (mm)	BC1036 (N=141)	Placebo (N=148)	P value
Day 7			0.33*
Mean	−10.4	−7.9	
SD	18.93	18.82	
n	136	142	
Day 14			0.69*
Mean	−12.2	−11.0	
SD	23.28	21.34	
n	137	142	
Day 28			0.53*
Mean	−11.1	−9.3	
SD	23.39	23.70	
n	139	143	

Baseline is defined as Day 0. *, P value from analysis of variance (ANOVA) with factors treatment and centre without interaction. SD, standard deviation; VAS, visual analogue scale.

Cough VAS

Subjects in the BC1036 group assessed their cough as more severe at baseline compared to the placebo group, although the difference was not statistically significant (mean of 57.5±20.0 for BC1039 compared to 53.1±20.6 for placebo; P=0.066). At each timepoint during the study and at follow-up, a greater reduction in cough severity was seen in the BC1036 group compared to the placebo group, but again the difference was not statistically significant (*Table 2*).

Pulmonary function tests

At baseline, the pulmonary function tests were similar in the two groups: mean FEV_1 was 2.7±0.8 L for BC1036 and 2.6±0.7 L for placebo, mean FEV_1 predicted (%) was 99.0%±99.7% for BC1036 and 97.1%±96.4% for placebo, and mean FVC was 3.4±1.0 L for BC1036 and 3.4±0.8 L for placebo. There were no significant changes in lung function during the study period.

Safety

During the study, 50.5% of subjects experienced 290 AEs (53.9% BC1036, 47.3% placebo), the majority of which were mild or moderate intensity. Of these, a total of 111

Table 3 Adverse events

Total number of adverse events	Number of subjects/%/event count		
	BC1036 (N=141): 76/53.9/158	Placebo (N=148): 70/47.3/132	Total (N=289): 146/50.5/290
Most commonly reported adverse events			
Headache	18/12.8/25	10/6.8/12	28/9.7/37
Nasopharyngitis	8/5.7/8	9/6.1/9	17/5.9/17
Cough (worsening)	7/5.0/8	9/6.1/9	16/5.5/17
Total number of treatment-related adverse events	32/22.7/65	27/18.2/45	59/20.4/110
Most commonly reported treatment-related adverse events			
Headache	15/10.6/20	7/4.7/9	22/7.6/29
Nausea	4/2.8/6	2/1.4/5	6/2.1/11

Cell numbers represent the number of subjects, then the percentage of subjects with each event, and then the total number of events.

AEs in 59 subjects were considered drug-related (66 BC1036, 45 placebo) (*Table 3*).

Discussion

There are inherent difficulties in conducting cough studies. Cough is a unique symptom which can be under voluntary control (14). Marked heterogeneity in therapeutic response may be seen, dependent on disease type and severity (15). There is a significant placebo effect (up to 85%) associated with over-the-counter cough medicines (14), with this being due to natural recovery, measures of cough severity declining over the course of the trial (regression of cough response toward the mean), the demulcent effect of treatment, and the effect of the sweetness of the cough syrup in soothing cough (14). This is further enhanced by expectation of effect related to advertising, brand, packaging and formulation (14).

There are a number of methods used to measure cough frequency, intensity and severity, and reporting of cough is notoriously unreliable. Subjective measures of cough introduce considerable bias as the outcome relies on individual perception, which can be affected by environmental and psychological factors (16). Although cough scores using diary cards and VASs are widely used as an outcome measure, they are generally inaccurate because they rely on the motivation and vigilance of the subject, and do not consistently correlate with objective methods, such as ambulatory cough monitoring (17). Objective measurement of cough frequency using ambulatory electronic monitors

is currently considered to provide greater insight into the reduction of cough frequency (18). At the time this study was conceived, no viable/validated options were available. However, the development of equipment to achieve this has been the subject of much research in recent years. Recent software development has led to significant progress in the development of automated cough detection which largely overcomes the issues of what constitutes "a cough" for the purposes of counting. This should certainly be a consideration for future studies.

Theobromine has been suggested as a promising therapy for treatment of persistent cough. It has a rapid onset, long duration of activity (>4 hours), is substantially more effective than caffeine in inhibiting cough induced by citric acid in the guinea-pig model, and it is at least as effective as theophylline and doxophylline (4). Theobromine has also been shown to suppress capsaicin-induced cough in humans with no AEs, and is considered a novel and promising treatment which may pave the way for a new class of antitussive drugs (4).

This double-blind, placebo-controlled, parallel-group study investigated the effect of BC1036 (theobromine) on the QOL of subjects with persistent cough, with the primary efficacy endpoint being the change from baseline in LCQ score on Day 14. The results showed a greater effect on QOL following BC1036 treatment compared to placebo, but the difference was small and did not reach statistical significance and also did not meet the pre-determined limit for clinical significance that was set at a total LCQ score of 1.3 in the sample size calculation (13). However, for both

groups, mean scores were still in the moderately impaired range on the LCQ. For the cough severity score, a greater reduction in cough severity during the study was seen in the BC1036 group compared to the placebo group, but again the difference was small and not statistically significant. However, a confounding factor impacting these results was the finding that the treatment groups were not balanced at baseline, with subjects in the BC1036 group having a more severe persistent cough that had a greater impact on QOL at baseline compared to subjects in the placebo group. Although the statistical analysis was adjusted for baseline severity, the difference was too great to be corrected by modelling alone and thus was thought to impact on the overall results. Despite a post-hoc subgroup analysis, no reason was discovered for this baseline difference. Thus, for future studies, stratification at randomization for cough severity might be considered.

The results of this study highlight the difficulties of conducting cough studies. However, it should be noted that this was the first multicentre trial conducted in persistent cough and the largest trial in cough at the time it was conducted, and much has been learnt from this trial to guide subsequent studies. As improvements in understanding cough hypersensitivity are beginning to influence development of new cough preparations that are effective on all cough types (19), so it is important that future studies assessing cough use validated methods that are sensitive to change. Future trials must be conducted for an appropriate length of time, and details on extent of effects, adherence, and AEs should be reported using clinically relevant outcome measures, including cough frequency, severity and duration (20). One consideration for future trials could be to use composite endpoints which can bring about statistical precision and encompass the several different facets of cough assessment (21). However, any composite endpoint should not be too broad, thus rendering the results clinically meaningless (22). The dose may also have been a factor, as it was based on pre- and post-marketing experience of theobromine 300 mg capsules (Anycough™) which is approved in Korea. Further investigation is needed with regards to the potential for genetic polymorphisms of the metabolising enzymes and other factors that could influence drug metabolism.

In conclusion, this study showed that BC1036 was well tolerated and, although the primary endpoint did not achieve statistical significance, BC1036 showed a small but positive effect on improving subjects' QOL and also in reducing cough severity.

Footnote

Conflicts of Interest: AH Morice was chief investigator of this study. He has received speaker's honoraria from Astra Zeneca, Chiesi, Boehringer Ingelheim, Almirall, and Novartis. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, Astra Zeneca and Chiesi. L McGarvey was an investigator in this study, which was funded by Infirst Healthcare. ID Pavord has received speaker's honoraria in the last 5 years for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GSK and payment for organising an educational event from Astra Zeneca. He has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp and Respivert. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca and Napp. B Higgins was an investigator in this study, which was funded by Infirst Healthcare. KF Chung was an investigator in this study, which was funded by Infirst Healthcare. SS Birring has received personal fees from Infirst Ltd for scientific advisory boards and advice.

Ethical Statement: This study was performed in accordance with the Declaration of Helsinki. This human study was approved by National Research Ethics Services Committee North East - Sunderland (approval: 11/NE/0375). All

adult participants provided written informed consent to participate in this study.

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