Inhaled alkaline hypertonic divalent salts reduce refractory chronic cough frequency

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Shareable abstract (@ERSpublications)
Inhaled alkaline hypertonic divalent salt aerosol reduces cough frequency in refractory chronic cough patients with baseline cough rates in range 4–34 per h with highest control-adjusted efficacy (35% reduction) for pH 9 aerosol from 3 days post-dosing. https://bit.ly/3V8q1jr

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Abstract

Background Treatment of chronic cough remains a challenge. We hypothesised that inhaled alkaline hypertonic divalent salts (alkaline HDS) might provide relief for refractory chronic cough by laryngeal and tracheal hydration.

Methods We conducted an exploratory, single-blinded, nasal saline-controlled study in 12 refractory chronic cough patients to examine cough suppression efficacy of an alkaline HDS composition (SC001) at pH 8 or pH 9 administered by nasal inhalation. As control, we used nasal saline with the same hand-held pump spray aerosol device. Each subject was monitored continuously using a digital cough monitor watch for 1 week of baseline, 1 week of control treatment and 1 week of active treatment.

Results Baseline daily cough rates ranged from 4 to 34 coughs·h^{-1} with mean visual analogue score 65±17 pre- and post-baseline testing. Control-adjusted efficacy of cough rate reduction ranged from 15% (p=0.015) (from Day 1) to 23% (p=0.002) (from Day 3). Control-adjusted efficacy was highest with SC001 pH 9 (n=5), ranging from 25% (p=0.03) (from Day 1) to 35% (p=0.02) (from Day 3), and lowest for SC001 pH 8 (n=7), ranging from 9% (p=0.08) (from Day 1) to 16% (p=0.02) (from Day 3). Hourly cough counts and visual analogue score correlated for baseline (r=0.254, p=0.02) and control (r=0.299, p=0.007) monitoring weeks. Treatment improved this correlation (r=0.434, p=0.00006). No adverse events were reported.

Conclusions Alkaline (pH 9) HDS aerosol is a promising treatment for refractory chronic cough and should be further evaluated.

Introduction

Chronic cough afflicts ~10% of the human population with a high morbidity and is currently without effective treatment [1]. It may be associated with an underlying condition, such as asthma [2], or without apparent underlying condition [3]. A cough hypersensitivity syndrome with frequent occurrence of symptoms associated with laryngeal hypersensitivity is likely to form the basis of most chronic cough subjects, with evidence for both peripheral and central pathway involvement of the airway–brain axis [4].

The hydration status of the surface liquid of the larynx and trachea may regulate the activity of peripheral cough receptors and therefore rehydrating and de-acidifying the larynx and trachea with hydrating aerosols may represent a treatment for chronic cough [5].

Hypertonic divalent salts (HDS) of calcium and magnesium chloride, with large droplet size (8–15 µm), inhaled through the nose or mouth, hydrate the larynx and trachea significantly longer than sodium chloride based on measurements of phonation threshold pressure [6] and exhaled breath particles [7, 8]. By lacking the permeating cation (sodium) and including the permeating anion (chloride) [6], HDS further avoids the acidity-provoking nature of hypertonic normal saline and hypertonic mannitol, used in cough challenge studies [9, 10]. Upper airway-targeted HDS aerosols reduce airway surface liquid (ASL) compression of airway epithelial cells [11], thereby reducing ATP secretion into the ASL [12], with upregulation of CFTR protein [13, 14] *via* reduction in intracellular calcium [15, 16, 17] facilitating ASL de-acidification. Buffering alkaline HDS with physiological buffers to high pH may therefore further permit more rapid elevation of ASL pH in acidic upper airways.

Monitoring of cough has historically been patient-reported [18], while a single-day audio-recording of cough counts has been used as a clinical outcome measurement [19], usually performed prior to treatment and at the end of the course of treatment [19, 20]. Recently, continuous cough monitoring has become feasible with the use of machine learning to detect cough [21], and provided rich information potential in the hour-by-hour daily patterns of cough [22, 23].

We conducted an exploratory study in refractory chronic cough to examine the efficacy of an alkaline HDS aerosol (SC001) in a 3-week study with each subject serving as his or her control. We buffered SC001 to achieve either high alkalinity (pH 9) or low alkalinity (pH 8) to explore its importance in the overall efficacy of laryngeal hydration. We evaluated control-adjusted efficacy with the primary outcome of daily cough count suppression.

Methods

Active and placebo compositions

SC001, a hypertonic solution of 4.1% (weight/volume) calcium chloride ($CaCl_2$) (Fisher Chemical, USA) and 0.82% magnesium chloride ($MgCl_2$) (Spectrum Chemical, USA), was prepared by dissolving 4.92 g of the salts (total salt mass) in 100 mL of high purity water (Thermo Scientific, USA). Alkalinity was achieved by dissolving 0.0034% sodium bicarbonate ($NaHCO_3$) and 0.0024% sodium hydroxide (NaOH) into the salt solution. This buffer was chosen to permit a variable pH (±2) over 2 months of room temperature (25°C) shelf stability but with a relatively constant pH (±0.2) (within the range of 7.5 to 9.5) over the period of a single week of administration. Subjects in the study therefore received either a high alkalinity aerosol (pH 9±0.2) or a low alkalinity aerosol (pH 8±0.2) by receiving their SC001 composition at different weeks of formulation shelf stability (see supplementary material). We prepared the nasal saline control composition as follows: an isotonic solution of sodium chloride was prepared by dissolving 0.9 g of NaCl (Fisher Bioreagents, USA) in 100 mL of high purity water.

Active and placebo pump spray inhaler and aerosol design

We used the same pump spray inhaler to deliver both active and control compositions. The inhaler, widely used in pharmaceutical and cosmetic nasal and oral aerosol products in the USA and EU, was manufactured by AeroPump (Hochheim am Main, Germany) and supplied by Ursatec (Tholey, Germany). We chose a mesh diameter of 9 µm for the design of the active inhaler such that manual hand-held pump action produced a mass median aerodynamic diameter (MMAD) size of ∼13 µm (see supplementary material). This permitted inhalation delivery of the aerosol to the larynx and trachea while with negligible mass penetration beyond the carina. We chose a mesh diameter of 13 µm for the design of the nasal saline inhaler such that manual hand-held pump action produced an MMAD of ∼20 µm to avoid penetration into the larynx when used as a nasal delivery control.

Study participants

Participants were recruited from the chronic cough clinic at the Royal Brompton Hospital, London. We enrolled 14 subjects aged 30–70 years with a diagnosis of refractory chronic cough for at least 6 months, as determined by the European Respiratory Society diagnostic pathway, and a visual analogue scale (VAS) score >40 mm (ranging from 0 to 100 mm, with 100 indicating severe debilitating cough). Two participants dropped out before the conclusion of the study owing to insufficient cough (<3 coughs·h^{-1}) and illness. Participants were excluded based on a history of recent respiratory tract infection within 3 weeks, a concomitant diagnosis of underlying airways disease or vocal cord disorder, a forced expiratory volume in 1 s (FEV_1) <70% predicted, a history of current smoking/ex-smokers with >10 pack-year history and long-term use of angiotensin-converting enzyme inhibitors and immunosuppressive treatments.

This study was approved by the HRA and Health and Care Research Wales through a submission to the Integrated Research Application System (Protocol number: 22IC7941). All participants gave informed signed consent to participate.

Study design

In this exploratory, single-blinded, placebo-controlled study, 12 subjects attended for four visits over a 3-week period between April and November 2023 (figure 1). Cough count was recorded throughout the 3-week period with the Hyfe cough watch, together with daily recordings of the VAS cough score.

At screening (V1), enrolled participants were provided with a digital cough watch monitor to record 7-day continuous hourly cough counts during baseline (Week 1), while receiving control aerosol (nasal saline, Week 2) and active aerosol (SC001, high or low pH, Week 3). Participants were trained to ensure correct use of the digital cough watch monitor and pump spray inhalers, in ∼5-min sessions, and each participant received a 1-min aerosol device demonstration video. Participants self-administered the nasal saline and active aerosol four times per day: on awakening, around noon, around dinner time and prior to sleep. Participants confirmed dosing times each day during control and active weeks. Participants were blinded as to whether they received active or control aerosol, with no taste or smell associated with either the active or the control treatment. The trial ended on the last days of dosing of the 12th subject.

Sample size was determined from the previous study of orvepitant, a neurokinin-1 receptor antagonist, in 13 participants with chronic cough where there was a 26% reduction in hourly cough rate obtained from the 24-h cough count measured before and at the end of each of the 4-week study periods [1, 24]. We reasoned that 12 participants would be sufficient to show an active effect on the cough rate in our study at an even greater power given that 1) there would be a control placebo period and 2) we would be measuring daily cough counts throughout the 21-day study period. We also determined *post hoc* the sample size by the power analysis that is provided along with the full trial protocol in the supplementary material. In this exploratory study, a randomised crossover design was not used, given the uncertainty in the washout time of the active treatment. Otherwise, we followed the CONSORT reporting guidelines [25].

Cough monitoring

Hourly cough rates were measured using a digital cough watch monitor containing the validated Hyfe Cough Research application (Hyfe, Wilmington, DE, USA) [21]. The Hyfe Cough Research app monitors ambient sound levels continuously, recording "explosive" sounds lasting <0.5 s, which are then analysed using a server-based convolutional neural network (CNN) model. This CNN model has been validated in differentiating between cough and non-cough sounds with high sensitivity and specificity (R). After processing, hourly cough data were then recorded on an online dashboard and downloaded into an excel spreadsheet for further analysis. The smart watch was worn every day for the entire 3-week period. At the end of each day, subjects were asked to remove the cough watch and place it on a charging stand in close proximity by their bedside, ensuring the watch continued to record coughs while charging and automatically uploading real-time cough data to the cloud. On awakening, subjects were instructed to place the watch back on the wrist for the entire day. Data uploaded onto the online dashboards was checked at regular intervals to screen for disruptions in cough monitoring and where possible, corrected. Days where no monitoring of cough data occurred are unreported in our data set as is any arm of the study where >50% of the days lacked monitoring (as occurred with one arm for one subject in the study). On days of partial monitoring a total count estimate was made by dividing measured counts by the hours of that day's monitoring and multiplying by 24. Days where subjects failed to administer the active treatment or where a subject fell ill were also not included.

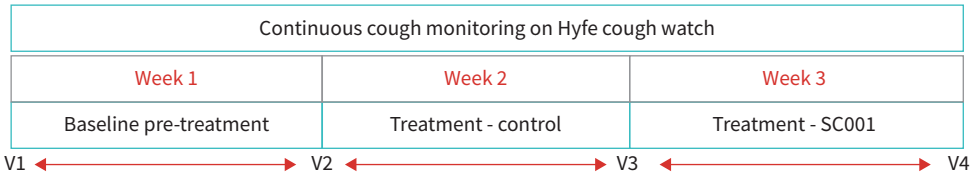

FIGURE 1 Design of the exploratory clinical study of alkaline hypertonic divalent salt (HDS) aerosol for refractory chronic cough treatment. At each visit (V1, V2, V3 and V4) participants were evaluated with clinical measurements as described in the Methods, but cough counts were recorded throughout the study using the Hyfe cough watch.

Control-adjusted efficacy determination with continual cough monitoring

We determined treatment efficacy of cough rate reduction relative to control for the entire group (n=12), and for each subgroup, as the mean of each participant's daily cough rate reduction over all treatment days relative to each subject's own control over all control days [26]. In our reporting of the data we identified baseline, placebo (or control) and active daily cough rates as b_{nd}, p_{nd} and a_{nd} respectively, for each subject n on each day d. Further detail and the entire set of digital cough data (b_{nd}, p_{nd}, a_{nd}, B_n, P_{nd}, A_{nd}, C_n) is available in the supplementary material.

Clinical measurements and exhaled breath sampling

During each visit, lung function tests were performed using a dry-wedge spirometer (Vitalograph, Buckinghamshire, UK), and fractional exhaled nitric oxide (F_{ENO}) concentrations were measured using a portable F_{ENO} monitor (NObreath; Bedfont Scientific Ltd, Rochester, UK) during a constant expiratory flow rate of 0.05 L·s^{-1}. Chronic cough symptoms and severity were assessed during each visit using the Leicester Cough Questionnaire (LCQ), Laryngeal Hypersensitivity Questionnaire (LHQ) and VAS [1–3]. Participants were also provided with a diary to complete daily VAS measurements. Exhaled breath condensate (EBC) was collected using the commercially available EBC collector (ReDi, EBC Condenser v1.0) [27]. Participants were asked to perform tidal breathing into the device for 10 min through a mouthpiece, after which ∼200–400 µL of condensate was collected *via* pipette into an Eppendorf tube. pH was measured *via* a bench top pH meter (FiveEasy Plus pH meter FE20, Mettler Toledo) using a calibrated electrode (pH electrode Mettler LE422 micro gel, Mettler Toledo).

Statistical analysis

We calculated the mean hourly and daily cough counts for each subject at baseline, and during control and active treatment periods. Mean daily cough counts during control and active treatment periods were adjusted for each subject by dividing this by their mean daily cough count at baseline monitoring. Baseline- and control-adjusted efficacy was calculated for each subject as the percentage reduction in mean cough during the treatment arm in relation to baseline/placebo. Inter- and intra-subject daily cough counts were compared using the single-tailed t-test. Daily cough counts were correlated to VAS using Spearman's rank correlation coefficient. p-values <0.05 were deemed statistically significant. Statistical tests and graphs were performed and created using Python programming (version 3.12.1) and Excel (Microsoft 2010).

Results

Baseline participant demographics and cough distribution

Participants in the study were predominantly female (n=9, 75%), consistent with previous studies [19, 20], with a mean age of 57.3 years (range 35–68 years) as summarised in table 1. Mean total LCQ and LHQ scores on the screening visit were 10.6 (range 6.3–17) and 13.9 (range 7.6–20.0), respectively. Mean baseline VAS score was 65.2 mm, suggesting a perceived moderate–severe symptom burden. FEV_1, FEV_1/forced vital capacity ratio and F_{ENO} were within normal limits.

Mean cough rate (figure 2), as determined from the first week of baseline monitoring, ranged from 4 coughs·h^{-1} to 34 coughs·h^{-1}. Nine out of 12 subjects had a mean daily cough rate below 20 coughs·h^{-1}, while all 12 coughed above 20 coughs·h^{-1} for at least 1 h; the three subjects with highest cough rate (8, 11 and 12) frequently coughed in excess of 100 coughs·h^{-1}. Mean day-time (07:00 to 22:00) cough counts for the 12 subjects predominated over night-time cough counts, while night-time cough characterised the experience of all 12 subjects. We found a significant positive correlation (figure 3) between hourly cough counts and VAS score for all 12 subjects across all days of baseline counting (r=0.254, p=0.02), control counting (r=0.299, p=0.007) and treatment counting (r=0.434, p=0.00006). We found no positive correlation between hourly cough counts and LCQ/LHQ scores during baseline, control or active periods (supplementary figures S5 and S6).

Treatment by alkaline HDS improves with dosing days and degree of alkalinity

Self-administration of the alkaline HDS (SC001) aerosol reduced daily cough rate relative to control for the group from Day 1 over the week of active dosing by 15% (p=0.015). This efficacy increased by Day 3, reaching 23% from Day 3 (p=0.002) and Day 4 (p=0.003) (figure 4). Those subjects (n=5) who self-administered the highest alkaline HDS (SC001pH 9) responded with the highest control-adjusted efficacy of 25% (p=0.03) from Day 1. Control-adjusted efficacy for SC001 pH 9 increased to 35% from Day 3 (p=0.02) and 33% from Day 4 (p=0.01) (figure 4). Control-adjusted efficacy for those subjects (n=7) who received the lowest alkaline HDS (SC001 pH 8) ranged from 9% (p=0.08) (from Day 1) to 16% (p=0.02) (from Day 3) and 17% (p=0.02) (from Day 4) (figure 3). Control-adjusted efficacy did not significantly change (p>0.5) post Day 3 of active daily administration for the entire group nor for the

TABLE 1 Subject demographics

Age years	60.00 (52.75–65.50)
Sex	
Female	9 (75)
Male	3 (25)
BMI kg·m^{-2}	24.85 (21.12–26.40)
Race	
Black	1 (8.3)
Mixed white and Asian	1 (8.3)
White	10 (83)
LCQ score	10.03 (9.18–11.33)
LHQ score	15.04 (10.58–16.12)
Baseline VAS	60.50 (49.50–77.75)
FEV_1 % predicted	99.50 (85.50–107.50)
F_{ENO} ppb	15.17 (11.14–37.37)
Comorbidities	
Chronic pain	1 (8.3)
Chronic rhinitis	1 (8.3)
Hypertension	1 (8.3)
None	9 (75)
History of atopy	
No	12 (100)
Current medications	
Amitriptyline	1 (8.3)
Gabapentin	2 (17)
None	9 (75)
Previous neuromodulator	12 (100)

Data are presented as median (IQR) or n (%). BMI: body mass index; LCQ: Leicester Cough Questionnaire; LHQ: Laryngeal Hypersensitivity Questionnaire; VAS: Visual Analogue Scale; FEV_1: forced expiratory volume in 1s; F_{ENO}: fractional exhaled nitric oxide.

subgroups. Diminution of mean daily cough rate during the saline control week for all subjects (n=12) relative to mean baseline cough rate was 4% ($p<0.05$). No adverse events were reported.

Weekly VAS fell post the treatment week relative to post the control week for four of the five subjects who received the high pH alkaline HDS aerosol (figure 5). Weekly VAS increased by 14% for Subject 2, who failed to administer the active aerosol on the final 2 days of treatment. These trends were matched by daily VAS as expressed as the mean of the last 3 days of treatment relative to the last day of control (figure 5). Daily VAS values for all five of the high pH aerosol-treated subjects are shown, as are daily VAS values for all subjects (supplementary figures S3 and S4).

An acute response to SC001 treatment appeared in the hourly cough rate responses of the eight out of 12 subjects who recorded their dosing intervals, with hourly cough rate tending to fall for 3 h post-administration as shown in supplementary figures S6 and S7. No significant inter-subject change was observed in EBC pH from post-control (7.27±0.27) to post-treatment (7.37±0.27), while EBC pH increased post-treatment relative to control for nine of the 12 subjects (supplementary figure S7).

Discussion

In this exploratory single-blinded nasal saline-controlled clinical study of 12 refractory chronic cough subjects, inhalation of alkaline HDS (SC001) reduced daily cough rate by 15–23% relative to control saline across the entire mean baseline cough rate range of 4·to 34 coughs·h^{-1} with a trend to elevated efficacy after each day of self-administration up to Day 3. Control-adjusted efficacy among those five subjects who self-administered the highest alkalinity HDS (pH 9) was 25–35% from the first to the third day of dosing, while the other seven subjects who self-administered the lowest alkalinity HDS (pH 8) responded with significant efficacy from Day 3 of treatment (16%, p=0.02). These findings, albeit the results from a small, exploratory, single-blinded study, are comparable to those (19% to 34%) achieved in Phase 2b studies with the P2X3 antagonists gefapixant and camlipixant at oral doses of 50 mg, but they indicate efficacy across a broader range of refractory chronic cough experience, notably above and below the cough rate (20 coughs·h^{-1} or 25 coughs·h^{-1} wake-time) beneath which the P2X3 antagonists appear inefficacious [19, 20]. Alkaline HDS aerosols also provide an unusual safety profile, being entirely endogenous to the

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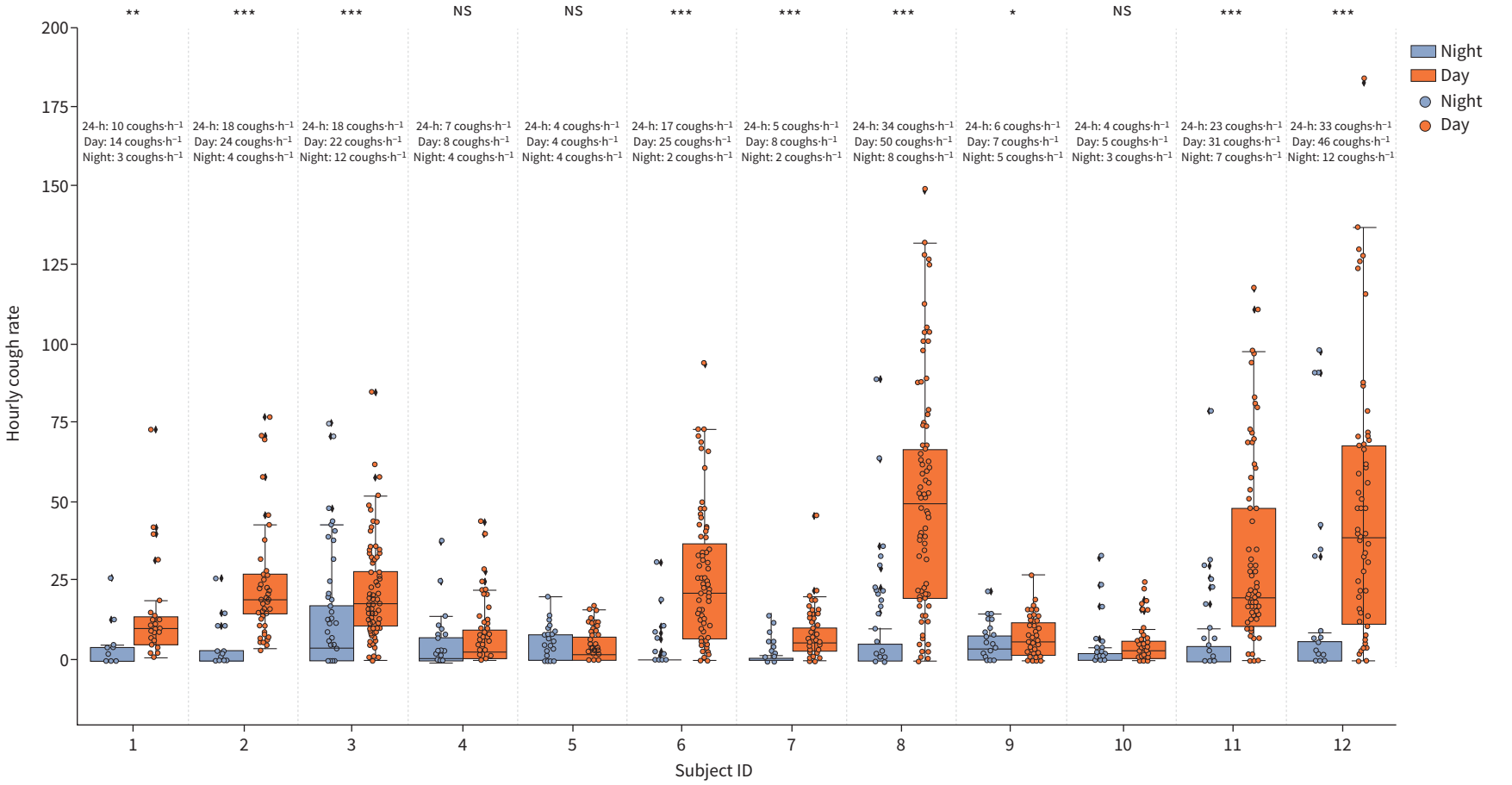

FIGURE 2 Box plot showing the hourly cough count distribution and daily-averaged mean and median hourly cough rate during the baseline monitoring period for the day and night hours. Each box plot shows the median, interquartile range (IQR), maximum and minimum values, with each round marker representing the total number of coughs measured for every hour monitored. NS: not significant; *p<0.05; **p<0.01; ***p<0.0001.

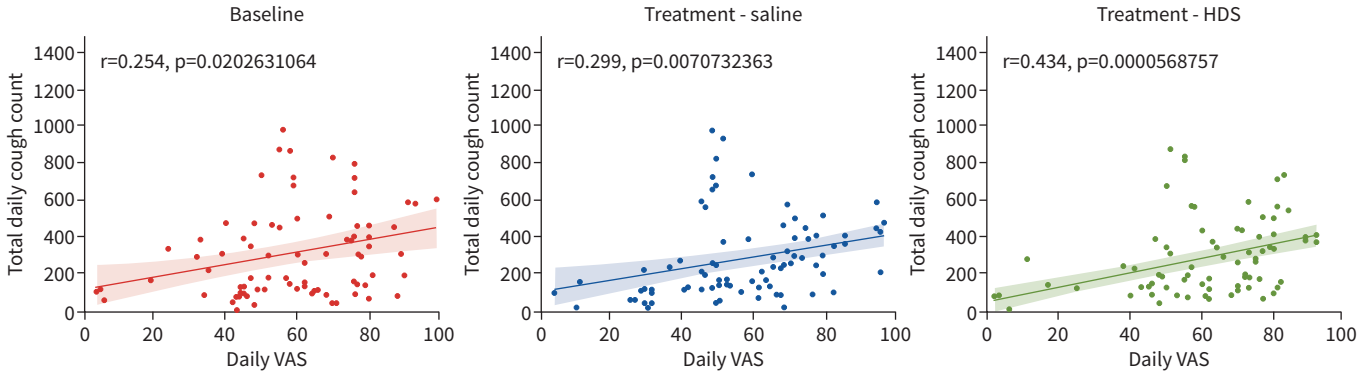

FIGURE 3 Scatterplots showing positive correlations between daily visual analogue scale (VAS) measurements and total daily cough count for subjects during the baseline, control and treatment phases. HDS: hypertonic divalent salts.

airways, and with HDS doses (~30 mg solution per dose inhaled, and ~6 mg solution per dose laryngeal deposited) around 100 times less than recommended calcium or magnesium salt oral supplements.

The use of continuous cough monitoring permitted determination of treatment effect over multiple days of treatment relative to multiple days of control rather than *via* a single day of treatment relative to a single day of control as in previous clinical studies of refractory chronic cough treatment [19, 20]. This proved pivotal in the identification of progressive efficacy improvement with days of treatment, while it also avoided flaws associated with the instability of daily cough counts. Notably, while over the full week of control the control effect for the group was small, with 4% cough rate suppression, on the last day of control testing (Day 6), the mean control cough rate for the group increased relative to baseline by 17%, while on Day 5 mean control cough rate for the group decreased relative to baseline by 9%.

Our results suggest the possibility that laryngeal dehydration may be an underlying condition of refractory chronic cough, consistent with a mucus transpiration inflammatory (MDI) pathway [11]. Inflammation by mucus transpiration is activated by relatively high evaporation rate in the vicinity of the larynx and trachea,

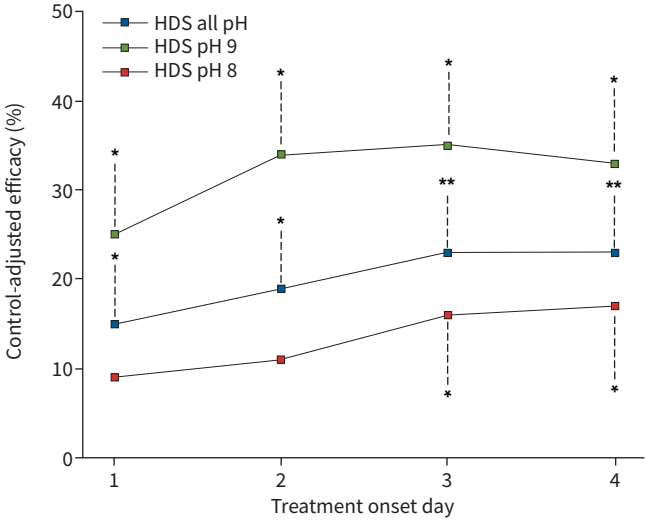

FIGURE 4 Nasal saline control-adjusted efficacy as a function of assumed day of treatment onset up to Day 4 following first administration after which no significant efficacy change occurs for the entire treatment week. Efficacy of treatment is represented for all subjects (n=12) treated with the alkaline hypertonic divalent salts (HDS) aerosol (SC001) and for those subsets of subjects treated with pH 9 HDS (n=5) or pH 8 HDS (n=7). *: 0.01<p<0.05; **: 0.001<p<0.01.

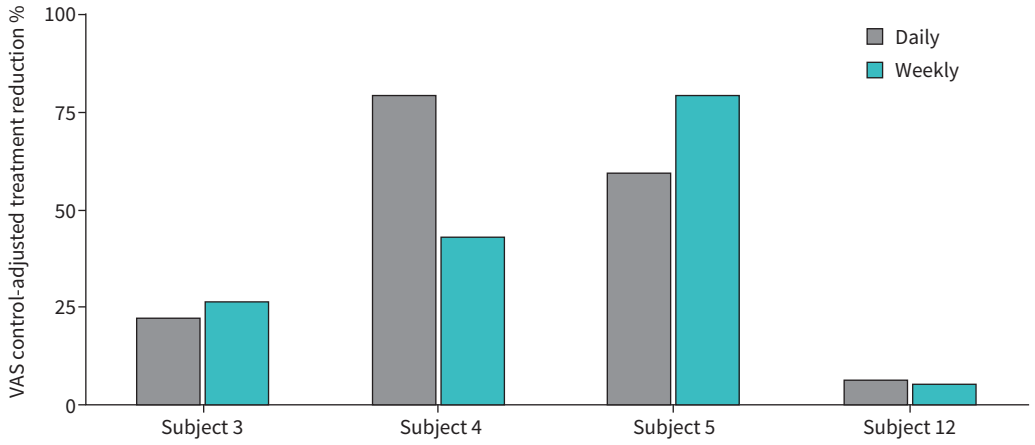

FIGURE 5 Per cent reduction in weekly and daily visual analogue score (VAS) post-treatment relative to post-control for the four subjects who received the high alkaline hypertonic divalent salts (HDS) aerosol and successfully administered the aerosol for the entire week of treatment. Per cent VAS reduction for daily VAS is based on the mean VAS of the last 3 days of treatment relative to the VAS of the last day of control testing.

leading to elevated pressure within the ASL [5, 11]. Compression of airway epithelial cells promotes secretion of ATP and P2X3-mediated cough provocation [5]. Prolonged ATP elevation further downregulates CFTR protein in the apical membrane of airway epithelial cells, apparently by mutually exclusive protein kinase A (PKA)- calmodulin-mediated processes [13], lowering bicarbonate secretion into the ASL, reducing buffer capacity and potentially eliciting cough by a second pathway, *via* stimulation of TRPV1 and ASIC receptors [11–17]. Inhalation of alkaline HDS droplets of median aerodynamic diameter 13 µm reduces laryngeal/tracheal epithelial cell compression thereby reducing inflammation and providing two inter-related mechanisms of action for cough reduction, potentially effective at F_{ENO} levels higher than those (<25 ppb) characteristic of participants in the present study.

VAS and hourly cough rate correlated across baseline, control and active treatment weeks, with greatest correlation during the active treatment week (figure 3). These trends are in alignment with previous efficacious treatment studies [19, 20], where VAS has been reported to significantly fall with cough rate from 4 weeks of treatment and beyond [19].

Further studies are required to confirm the conclusions of our study with alkaline HDS pH 9 in a double-blinded, randomised, placebo-controlled clinical trial in refractory chronic cough patients following the size recommendation of the power analysis that is provided in the supplementary material based on the results of this exploratory study. While nasal administration provides potential secondary benefits to laryngeal hydration by maintaining nasal cavity hydration during tidal breathing, direct laryngeal delivery *via* oral dosing should be explored. Confirmation of onset of action, clarification of washout period post-alkaline HDS treatment, elucidation of treatment efficacy relative to baseline cough rate by longer duration of treatment, and assessment of ASL pH and inflammation with treatment should be pursued. Confirmation of long-term safety profile is also needed. Understanding at a molecular and cellular level the impact of HDS deposition on purinergic signalling and CFTR expression in the apical airway epithelial membrane with sustained suppression of ASL ATP will be critical to clarifying the mechanism of action and optimising HDS therapy. Finally, correlation of cough incidence and HDS aerosol efficacy with environmental triggers, including temperature, relative humidity and $PM_{2.5}$, as is facilitated by continuous cough monitoring, may begin to deepen understanding of the environmental origins of chronic cough and be beneficial to antitussive development more generally.

Our study suggests the possibility for a safe and efficacious treatment of refractory chronic cough, with potential acute and chronic benefit, and cough suppression efficacy within a broader range of cough experience. Alkaline HDS aerosols should be pursued as a potential first-line treatment for refractory chronic cough. Such aerosols, by suppressing triggers of cough that cough-receptor antagonist drugs aim to block, might also be useful as receptor-targeting drug adjuvants.

Provenance: Submitted article, peer reviewed.

Data availability: All the individual participant data, deidentified, are available through the various links in the supplementary material.

Ethics statement: This study was approved by the HRA and Health and Care Research Wales through a submission to the Integrated Research Application System (protocol number 22IC7941). All participants gave informed, signed consent to participate.

Conflict of interest: H. Abubakar-Waziri has no conflicts to report. D.A. Edwards and D.B. Bhatta are founders and employees of Sensory Cloud Inc., the manufacturer of SC001. J.H. Hull is an associate editor of this journal. M. Rudd and P. Small are consultants to and employees of Hyfe Inc., the manufacturer of the digital cough monitor watch. K.F. Chung has received honoraria for participating in advisory board meetings of Roche, Merck, Shionogi and Rickett-Benckiser, and has been renumerated for speaking engagements for Novartis and AZ. K.F. Chung is also Scientific Adviser to Hyfe Inc. and Sensory Cloud Inc.

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