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Efficacy and Tolerability of Zinc Acetate for Treatment of Chronic Refractory Cough: Pilot Randomized Futility Trial

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Abbreviations

ALA	American Lung Association
ACRC	Airways Clinical Research Centers
CQLQ	Cough Quality of Life Questionnaire
C-VAS	Cough Visual Analog Score
EQ-5D-5L	EuroQol questionnaire
FDA	Food and Drug Administration
GACC	Global Assessment of Change in Cough
GERD	Gastro-oesophageal reflux disease
LCQ	Leicester Cough Questionnaire
MCID	minimum clinically important differences
ZICO	Zinc Acetate to Improve Chronic Cough

Abstract

Background

Cough is the most reported symptom in the US, with chronic refractory cough representing significant morbidity to patients. Zinc acetate may have beneficial effects in the cough reflex pathway.

Research Question

We sought to assess the safety and efficacy of zinc acetate in the management of chronic refractory cough.

Study Design and Methods

This was a randomized, placebo-controlled, parallel design pilot trial of individuals with chronic refractory cough. The effects of six weeks of zinc acetate versus placebo on quality of life and symptoms as measured by the Cough Quality of Life Questionnaire (CQLQ), Leicester Cough Questionnaire (LCQ), Cough Visual Analog Score (C-VAS), and Global Assessment of Change in Cough (GACC) scores were evaluated. A futility analysis plan with a one-sided 80% confidence interval was used to compare treatment effect to published minimum clinically important differences (MCID) for each outcome.

Results

A total of 34 participants, 17 in each group, were enrolled and randomized. Participants were primarily White females with moderate-severe cough. Participants assigned to zinc acetate had a significant increase in serum zinc levels after 6 weeks while those assigned to placebo did not. Both groups showed improvement in CQLQ, LCQ, C-VAS, and GACC scores, but the treatment effects of zinc acetate versus placebo were small with confidence intervals that did not include the MCIDs.

Interpretation

We observed no benefit of zinc therapy over placebo on cough symptoms or quality of life and conclude that larger trials of zinc for chronic cough are not warranted.

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Introduction

Cough has been reported as the most common symptom leading to physician office visits, occurring in 9-12% of the population and accounting for nearly 20% of pulmonary specialty referrals[1–4]. Chronic refractory cough is defined as a cough lasting more than eight weeks that occurs in the absence of inhalational irritation, medications, heart failure, or parenchymal lung disease, that does not resolve with treatment for airway disease, gastroesophageal reflux disease (GERD), or sinusitis. It is a challenging condition that is associated with profound impairment of patients' quality of life, increased social isolation, and sleep disturbance[5,6]. Despite some evidence of improvement in patient-reported outcomes with use of several repurposed medications aimed at targeting cough reflexes, such as anti-convulsants, anti-depressants, or narcotics, many of these medications have significant side effects and potential for abuse[7–12]. Currently, there are no licensed drugs available for treatment of chronic refractory cough although P2X3 antagonists have shown some promise.

Considerable progress has been made in understanding the pathways and receptors regulating cough, and this has facilitated the identification and evaluation of novel therapeutic strategies for cough suppression[13,14]. Notably, cough receptors uniquely express isozymes of Na+-K+ ATPase, which regulate cough receptor excitability[15]. Selective neuronal sodium pump inhibitors therefore offer a potential therapeutic avenue for management of chronic cough. Zinc and other electrophilic metals inhibit Na+-K+ ATPase with some selectivity for neuronal isoforms[16–18]. Zinc is also an anti-oxidant that prevents mucus secretion in the airways and inhibits inflammation[19]. Previous work in a guinea pig model demonstrated the efficacy of zinc as a potential anti-tussive treatment, when applied topically to the airways mucosa, relaxing tracheal smooth muscle[20]. Additionally, in humans, zinc lozenges have been shown to reduce the duration of upper respiratory infections and associated symptoms, in particular acute

cough[21–25]. Thus, we hypothesized that oral zinc may be a safe and effective anti-tussive treatment in chronic refractory cough.

We conducted the Zinc Acetate to Improve Chronic Cough (ZICO) study as a pilot trial of zinc acetate (Galzin®, Teva Pharmaceuticals) to determine its potential efficacy and tolerability as a treatment for idiopathic or refractory chronic cough. Our objective was to obtain preliminary evidence regarding the potential efficacy, measured by cough-related quality of life, as well as tolerability of zinc acetate. Additionally, the ZICO trial was designed to evaluate different measures of cough to help establish other potential outcomes for a larger trial. The trial was designed as a pilot futility study that would establish whether a larger definitive trial is warranted.

Methods

Design

ZICO was a randomized, placebo-controlled, parallel group pilot clinical trial comparing the effect of zinc acetate to matching placebo on the primary outcome Cough Quality of Life Questionnaire (CQLQ)[26]. The study was conducted by the American Lung Association – Airways Clinical Research Centers (ALA-ACRC) at five clinical sites. The protocol and consent statements were reviewed and approved by the institutional review boards at each of the sites.

Eligible participants were age 18 years or older with multiple daily episodes of cough persisting for more than three months and a score ≥30mm on a 100mm Cough Visual Analog Scale (C-VAS)[27]. Non-smokers or former smokers with less than 20 pack-years of exposure were eligible. Individuals with asthma, other eosinophilic airway disease, gastroesophageal reflux or sinusitis were eligible if treatment with inhaled corticosteroids and/or bronchodilators, H_2 blockers and/or proton pump inhibitors, or nasal steroids, antihistamines, expectorants, or decongestants, respectively, did not resolve cough. A chest x-ray or chest computed tomography scan within two years, and after the onset of cough, negative for parenchymal lung

diseases (such as interstitial lung disease, bronchiectasis, pneumonia, or TB) and negative for lung cancer was also required.

Major exclusion criteria included (1) tobacco or marijuana use in prior 6 months, (2) use of angiotensin-converting-enzyme inhibitors or zinc supplements in prior 6 weeks, (3) occupational exposures to dust or chemicals, (4) diagnosis of chronic obstructive pulmonary disease, congestive heart failure, or chronic kidney disease, (5) current pregnancy or lactation, and (6) history of bronchiectasis, interstitial lung disease, sarcoidosis, pneumoconiosis, asbestosis, chronic mycobacterial infection, lung cancer or pancreatitis.

Screening and follow-up

Potential participants were screened at the first visit and if eligible, additional baseline data and random assignment to treatment group were conducted at the second visit. Three additional in-person study visits were conducted at 3, 6 and 8 weeks. The 8-week visit was conducted after the study drug was discontinued (Figure 1).

Participants were instructed to complete a seven-item daily cough diary designed to assess patient-reported outcomes regarding frequency and severity of cough for the duration of the study[28]. At in-person visits the following questionnaires related to cough were administered: CQLQ[26,29], Leicester Cough Questionnaire (LCQ)[30–32], Cough Visual Analog Score (C-VAS)[27], and Global Assessment of Change in Cough (GACC)[32,33] as well as one general quality of life measure, EuroQol EQ-5D-5L[34,35].

Spirometry and clinical data on height and weight and medical history were collected at study visits. Blood specimens were collected at the screening visit and the 6-week visits for assessment of zinc levels. Because zinc impairs copper absorption, we also monitored copper levels to assess for potential copper deficiency syndromes.

Treatment

Treatment assignments were obtained from randomly ordered lists of assignments (permuted block design) with an allocation ratio of 1:1 stratified by clinical centre. Randomization tables were prepared and administered by the Data Coordinating Center. Participants were assigned to receive a daily dose of 150 mg of zinc acetate, taken in three doses of 50 mg each, or matched placebo. Oral zinc therapy was chosen in lieu of topical or lozenge formulations to avoid the adverse taste and smell which would preclude adequate masking for a placebo-controlled trial. The protocol was reviewed by the Food and Drug Administration (FDA) and determined to be exempt from Investigational New Drug regulations [21 CFR 312.2(b)]. The study used the FDA-approved formulation of oral zinc acetate, Galzin®. Galzin® 150mg/day is approved for long-term use in adults with Wilson's disease to reduce copper absorption. Zinc acetate capsules, 50 mg, were over-encapsulated and matching placebos were created. Participants were instructed to take the study drug with food in the morning or evening meal for 6 weeks and to titrate up the dose of study drug starting with one capsule (50 mg) in the morning on day 1, increasing to two capsules (100 mg) on day 4, and reaching three capsules (150 mg) on day 8. Participants unable to tolerate the full dose were instructed to titrate down to the highest tolerable dose. Participants were contacted by telephone 1 week after to randomization to assess tolerance to study drug.

Sample Size and Analysis Plan

The primary goal of the pilot study was to obtain preliminary estimates of the relative efficacy of zinc acetate versus placebo for reducing CQLQ scores at 6 weeks. A planned sample size of 36 (18 per group) had 80% power to detect a treatment effect of 0.56 standard deviations (SD) or greater based upon a two-sample t-test and a one-sided type 1 error rate of 0.20.

All analyses were conducted according to treatment assignment under an intention-to-treat principle and included all available data. A saturated linear means model with indicators for each time point, treatment and treatment by time interaction was used to estimate the treatment effect. The 6-week treatment by time interaction term represents the difference in change in CQLQ between the treatment groups. A random effect for individuals was used to account for the repeated measurements over time. Using the methods described by Cocks and Torgerson[36], we evaluated whether the upper boundary of the one-sided 80% confidence interval of the treatment effect excluded the minimum clinically important difference (MCID). If this were the case, then a larger trial would be deemed to be unlikely to detect an important treatment effect. Scores from other questionnaires were analysed using the same procedures. Data were analysed using SAS 9.4.

Results

Enrolment and Follow-up

A total of 34 individuals were randomly assigned to a study treatment, 17 per group, between February 2018 and October 2019 at 5 ACRC centres (Figure 2). The trial was ended before achieving the planned sample size of 36 because the masked study drug supplies expired at the end of November 2019. Follow-up in the treatment period was completed in all participants.

The participants were mostly middle-aged white women who never smoked cigarettes (Table 1). Baseline serum zinc and copper levels and pulmonary function were normal. Median body mass index (BMI) among participants was 28 kg/m^2, reflecting an overweight study population. A majority of participants were on treatment for GERD and sinusitis, and over 40% were also diagnosed with asthma. Sinusitis was more common among the participants randomized to zinc acetate than placebo.

Over two-thirds reported cough upon waking and about one-third reported persistent phlegm (Table 1). Furthermore, participants had moderate-severe impairment in quality of life as measured by CQLQ and LCQ scores and moderate-severe symptoms by C-VAS scores (Table 2). There were no notable differences in baseline cough assessments between participants randomized to zinc acetate compared to those assigned to placebo.

Safety and Tolerability of Zinc Supplementation

At study completion, most participants in both groups reported taking the full dose of 3 capsules per day, 94% and 88% for zinc and placebo respectively. Study treatment was terminated early in 1 and 2 participants assigned to zinc acetate or placebo, respectively. The participant assigned to zinc had a history of chronic pancreatitis and terminated treatment after 5 days due to acute pancreatitis. One participant assigned to placebo terminated treatment after 8 days because of a rash. Another participant did not initiate treatment because of health issues unrelated to the study. One participant receiving zinc acetate reported a skin rash 23 days after starting treatment. The rash improved with topical treatment without discontinuing study drug; it was reported as resolved at the participant's last visit. The participant contacted the site one year later to report ongoing severe skin rash and allergy to some of the inactive ingredients in Galzin based on patch testing.

Otherwise, the safety profiles were unremarkable. In the zinc acetate group, one participant experienced a skin rash that resolved in a few days, and one participant was admitted to the hospital for a surgical procedure unrelated to the study. Two participants assigned to placebo had elevated serum copper levels (178 and 177 mcg/dL). More information on reported serious adverse events is provided in Supplemental Table 1.

To establish whether supplementation with zinc acetate was effective in increasing circulating zinc concentrations, serum zinc levels were measured at baseline and 6 weeks after

randomization (Figure 3). Individuals randomized to zinc had an increase in median serum zinc concentration while individuals in the placebo arm had no significant change in serum zinc levels over the follow-up period. There was no significant difference between the changes in serum copper levels between the groups although the values increased in both groups (Figure 3).

Effect on Cough Scores

Quality of life improved, as measured by a decrease in mean CQLQ, over the study duration in both treatment groups, without evidence of rebound worsening during the washout period (Figure 4). Participants randomized to zinc acetate had a mean (95% confidence interval (CI)) improvement in CQLQ of -11.5 (-18.8, -4.4), while participants in the placebo arm had a mean (95% CI) for improvement of -8 (-15.5, -1.1) (Table 3). The mean and one-sided 80% confidence interval for the treatment effect was -3.5 (-7.7, ∞). Since the absolute value of the 80% confidence interval limit, 7.7 is less than the published MCID range of a decline of 11 to 15[37], the criterion for futility was met. Similar findings were noted for LCQ, C-VAS, and GACC scores; both treatment groups improved with small numerical differences in improvement that favoured for zinc but did not exceed published MCIDs for most scores[32,37–40]. The EQ-5D-5L, a general health quality of life measure, also improved in both groups, however, the difference favoured the placebo group and once again the upper bound of the 80% confidence interval did not exceed the published MCID[35].

Discussion

The ZICO trial was a pilot study designed to establish whether zinc acetate is a safe and promising treatment for chronic cough. We hypothesized that zinc acetate would improve patient-reported outcomes related to chronic cough based on positive results from studies using animal models for chronic cough and the wide-spread use of zinc-containing drugs for treatment

of upper respiratory-related symptoms[20–25]. Although mean improvements in scores observed exceeded the MCIDs for most measures in both the zinc acetate and placebo groups, the treatment effect of zinc acetate as compared to placebo were small and unlikely to exceed the minimal clinically important differences for these measures. We did not achieve the planned sample size of 38, however we do not think our estimates of the treatment effects were biased. A larger sample size would have likely led to narrower confidence intervals and would be unlikely to change our conclusion. The concordance of outcomes for multiple patient-reported outcomes supports the futility conclusion.

Zinc-containing drugs have been shown in some, but not all, studies to reduce the duration of acute cough associated with viral upper respiratory infections[21–25,41,42]. The effect may be related to blockade of acid-sensing ion channels[18,43], blockade of voltage gated ion channels[17], modulation of NMDA-type glutamate receptor channels[44] that may also be relevant to cough suppression[13], or neuronal sodium pump inhibition[16–18]. Drugs known to interact with sodium pumps dose-dependently suppress cough in guinea pigs and in patients[15,45,46]. However, many are nonselective, limiting their utility due to significant off-target effects. The neuronal selectivity of zinc for sodium pump inhibition offered promise for its therapeutic use, however, our results demonstrate that in a controlled comparison with placebo, despite adequate increases in serum zinc concentrations, the treatment effects associated with zinc acetate were very unlikely to be clinically important.

The population studied informs the interpretation of our results. We selected patients based on duration and severity of cough, in the absence of other chronic respiratory diseases, and failure to respond to specific treatment for co-morbidities such as gastroesophageal reflux, asthma, or sinusitis. As a result, our study results apply to patients with moderate to severe refractory chronic cough and we cannot exclude the possibility that zinc acetate is an effective treatment for less severe forms of cough or cough related to other aetiologies. The latter

consideration may account for the differences in our results compared to studies where zinc reduced acute cough related to upper respiratory infections. Additionally, it is possible that our results may be partially accounted for by the heterogeneity of the study population, reflected in the observed wide range of baseline CQLQ scores. Regardless, our population, although small and heterogenous, has similar demographics to other chronic cough populations[47–54], and represents individuals most in need of effective cough management therapies.

Additionally, the formulation of zinc therapy selected for this study is an important consideration. Prior studies examining zinc therapies for cough that have demonstrated benefit primarily used zinc lozenges[21,23,41,42]. Topical zinc has the potential for a greater increase in zinc concentrations at the target synapses within the larynx and pharynx than with oral zinc acetate; but has adverse effects on taste and smell and are not suitable for a placebo control. Oral zinc acetate was chosen for this study as it is already FDA-approved for another indication and is well-tolerated. Our results demonstrated that oral zinc acetate was effective in increasing serum zinc concentrations, with a two-fold increase in median serum zinc concentrations. However, it may be that we did not achieve high enough increases in serum zinc concentrations or adequate increases in airway zinc concentrations to demonstrate a beneficial effect. However, substantially higher doses of zinc may be associated with greater gastrointestinal adverse effects and higher risk of copper deficiency syndrome from chronic use.

Another consideration were the outcomes used in this study. The measures of cough relied on patient-reported symptoms and quality of life rather than more objective measures such as cough counts. This might be considered a weakness of the study, insofar as cough counts may be a more sensitive and responsive measure of cough suppression. However, using patient-reported outcomes in a masked pilot trial ensures clinical relevance; a reduction in cough counts without a benefit in patient symptoms and well-being would not be a clinically important outcome. Cough counts can be useful for testing proof-of-concept of novel cough

treatments, but ultimately outcomes that help patients should be examined and concurrent placebo controls are required for valid evaluations. This is particularly important given the substantial placebo effect in chronic cough trials.

A strength of this study was that we compared the effect of zinc acetate for several different patient-reported outcomes. The patient-reported outcomes included symptom and quality of life scores, both cough-specific and generic. We noted significant concordance between the different scores in ascertaining cough severity at baseline and change during the study. The consistent results demonstrating no significant treatment effect with zinc acetate compared to placebo across several cough outcome measures suggests that our negative finding was not the result of selection of an insensitive outcome measure. We also observed placebo-associated improvements in all measures with point estimates that met or exceed established MCIDs. Hence, caution should be used in evaluating improvement in cough symptoms over time in the absence of control groups.

In addition to assessing futility, we designed this trial to evaluate the safety and tolerability of zinc acetate. Zinc therapy is currently implemented in the management of patients with Wilson's disease[55]. As such, concerns about the potential effects of zinc acetate therapy on serum copper levels were considered. The dose and duration of zinc acetate in this trial did not induce copper deficiency, although higher doses and longer durations of treatment may have this effect.

In conclusion, the ZICO study established that while zinc acetate is a safe, well-tolerated treatment capable of increasing serum zinc concentrations in a few weeks, it is unlikely to elicit a substantial benefit for patients with chronic cough, and that a larger definitive study is very unlikely to show a beneficial effect of zinc for patients with chronic cough. Although this study was negative, the study design was efficient for real world evaluations of novel treatments for chronic cough. Our results also demonstrated a strong placebo effect and reinforce the

necessity of placebo groups in trials employing patient reported outcomes and using clinically important differences as a benchmark for establishing futility.

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Table 1: Baseline Characteristics			
Characteristic	**Total N=34**	**Zinc N=17**	**Placebo N=17**
Years of age, median (IQR)*	62 (52-70)	62 (56-70)	62 (48-67)
Female, n (%)	28 (82%)	12 (71%)	16 (94%)
Race			
White/Caucasian	28 (82%)	14 (82%)	14 (82%)
Black/African American	4 (12%)	2 (12%)	2 (12%)
Other	2 (6%)	1 (6%)	1 (6%)
Body Mass Index (BMI) median (IQR)	28.0 (23.6, 32.4)	27.9 (24.2, 31.9)	28.2 (23.6, 32.4)
Smoking status, n (%)			
Never	29 (85%)	15 (88%)	14 (82%)
Former	5 (15%)	2 (12%)	3 (18%)
Cough Characteristics, n (%)			
Cough upon waking	23 (68%)	11 (65%)	12 (71%)
Persistent phlegm in chest	12 (35%)	7 (41%)	5 (29%)
Conditions related to cough, n (%)			
Asthma - spirometry/methacholine	14 (41%)	8 (47%)	6 (35%)
GERD diagnosis or positive pH probe	20 (59%)	10 (59%)	10 (59%)
Sinusitis, postnasal drip, upper airway disease	20 (59%)	14 (82%)	6 (35%)
Spirometry, median (IQR)			
%Predicted pre-bronchodilator FEV_1	88 (84, 101)	95 (87, 102)	87 (83, 88)
%Predicted post-bronchodilator FEV_1	93 (83, 108)	101 (91, 108)	88 (81, 93)
Post-bronchodilator FEV_1/FVC	0.78 (0.73, 0.82)	0.78 (0.75, .81)	0.78 (0.73, 0.83)
Serum levels†, median (IQR)			
Zinc (mcg/dL)	82 (75, 92)	79 (69,92)	84 (79,92)
Copper (mcg/dL)	136 (116, 152)	130 (99, 148)	140 (132, 177)

*IQR – interquartile range

†Available for 32 participants

Table 2: Baseline Questionnaires Scores			
	Total N=34	**Zinc N=17**	**Placebo N=17**
Questionnaire, range, and abbreviation	**median (IQR)***		
Cough Specific Quality of Life (28-112) (CQLQ)	55 (43, 65)	57 (41, 65)	55 (46, 58)
Leicester Cough Questionnaire (3-21) (LCQ)	13 (9, 14)	14 (7,15)	12 (10,14)
Cough Visual Analog Scales (0-100) (C-VAS)	67 (45, 80)	67 (46, 77)	68 (43, 82)
Global Assessment of Change in Cough (-3-3) (GACC)	0 (-0.8, 0.0)	0 (-0.8, 0.0)	0 (-0.5, 0.0)
EuroQol EQ-5D-5L (0-1)	0.8 (0.5, 0.8)	0.8 (0.5, 0.8)	0.8 (0.5, 0.8)

*IQR – interquartile range

Table 3: Mean change from baseline in questionnaire scores				
Questionnaire, Direction of Improvement	**Zinc (N=17) LS Mean (95% CI)**	**Placebo (N=17) LS Mean (95% CI)**	**Zinc-Placebo 80% 1-sided CI**	**MCID***
CQLQ (⬇†)	-11.6 (-18.8, -4.4)	-8.3 (-15.5, -1.1)	-3.3 (-7.6, ∞)	-11
LCQ (⬆)	3.4 (1.5, 5.3)	2.8 (0.9, 4.7)	0.6 (-∞, 1.7)	1.3
C-VAS (⬇)	-16.1 (-30.0, -2.4)	-15.0 (-28.8, -1.2)	-1.2 (-9.3, ∞)	-13
GACC (⬆)	0.9 (0.2, 1.6)	0.8 (0.1, 1.4)	0.1 (-∞, 0.5)	NE
EuroQol EQ-5D-5L (⬆)	0.056 (-0.03, 0.142)	0.157 (0.07, 0.243)	-0.101 (-∞, -0.049)	0.051

Abbreviations: LS – least squares, CI – confidence interval, MCID – minimal clinically important difference, CQLQ – Cough Quality of Life Questionnaire, LCQ – Leicester Cough Questionnaire, C-VAS – Cough Visual Analog Score, GACC – Global Assessment of Change in Cough, NE-not established.

† Arrows (⬆ ⬇) indicating direction of improvement

* Minimum clinically important differences were obtained from published literature for CQLQ[37], LCQ[32,38, 39, 40], and C-VAS[32,38] and EQ-5D-5L[35]

Figure 1: ZICO Trial Design

Trial design included a baseline screening period (-1 to 0 study week) at the end of which participants were randomized. They then underwent titration over weeks 0 to 1 (dash-dot line). Figure inset describes the schema for titration with one pill, represented by blue oval, of either 50 mg zinc acetate or placebo from days 0-3, two pills on days 4-7, and 3 pills from day 8 onwards. Participants remained on this dose through the treatment period to week 6 and subsequently had a washout period (dash line) from weeks 6-8.

* Ineligible due to respiratory infection within 4 weeks

Figure 2: CONSORT Diagram

Figure 3. Serum Zinc Levels at Baseline and Follow-up by Treatment Group

Boxplots of serum zinc (left panel) and serum copper (right panel) levels at baseline and follow-up (week 5) by treatment group. The red boxes indicate the zinc treatment group and the blue boxes represent the group assigned to placebo. The lower and upper bounds of the box represent the 25^{th} and 75^{th} quartiles which is the interquartile range (IQR) with whiskers represent the minimum value or 1.5 x IQR if there are outliers. In the interior of the box, the solid line represents the median value. Individual values are represented by closed circles.

Figure 4: Cough Quality of Life scores at baseline, during follow-up, and after washout by treatment group.

Boxes represent the distribution of Cough Quality of Life Questionnaire (CQLQ) scores at different time points: baseline (week 0), during follow-up (weeks 3, 6), and after the washout period (week 8). The values at week 8 were at the end of the washout period after the assigned treatment was stopped. At each time point, the red boxes are for the zinc group and the blue boxes are for the placebo group. The lower and upper bounds of the box represent the 25^{th} and 75^{th} quartiles which is the interquartile range (IQR); in the interior of the box the solid line represents the median value; the whiskers represent the minimum or maximum values or 1.5 x IQR if there are outliers; each value is represented by a circle.

Supplemental Table 1: Adverse Events, Serious Adverse Events, Unanticipated Problems		
Treatment Arm	**Number of Participants**	**Description**
Zinc	1	Stopped medication within 5 days of drug initiation for pancreatitis thought unrelated to study medication due to known history of chronic pancreatitis
Zinc	1	Herniated lumbar disc requiring hemi-laminectomy
Zinc	1	Rash developed after over 3 weeks of treatment, improved after 3 days with topical treatments, study treatment was not discontinued and the rash was reported as resolved at the final study visit. However, patient contacted site 1 year later to inform them that rash increased in severity after completing the study. Participant underwent patch testing for sensitivities and showed reactions to inactive ingredients in Galzin.
Placebo	2	Elevated copper levels (178 mcg/dL and 177 mcg/dL; normal range 70-175 mcg/dL)
Placebo	1	Rash and itching, stopped study drug

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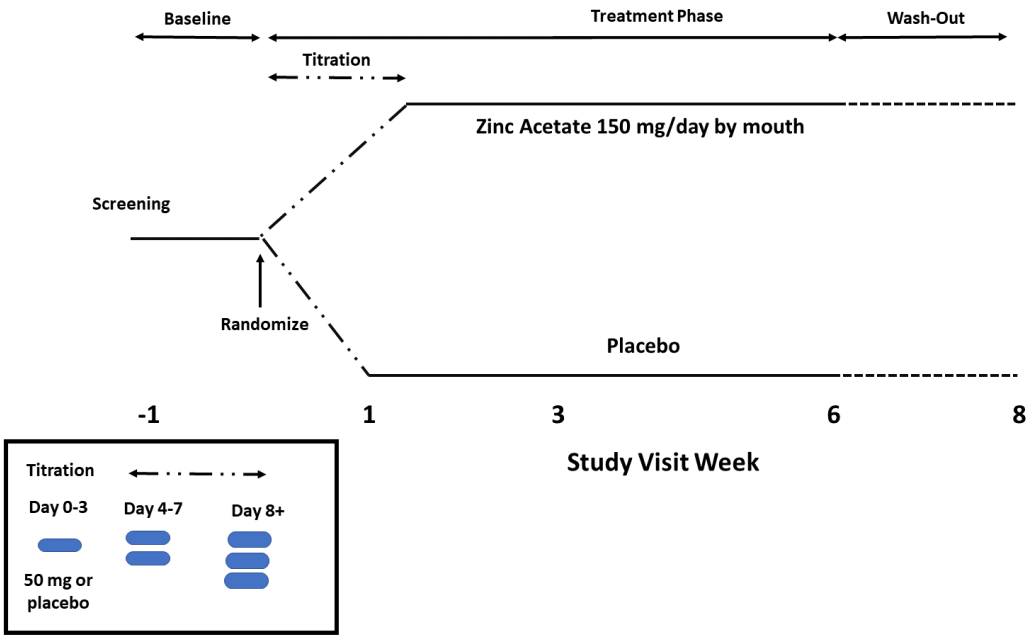
Baseline
Treatment Phase
Wash-Out
Titration
Zinc Acetate 150 mg/day by mouth
Screening
Randomize
Placebo
-1
1
3
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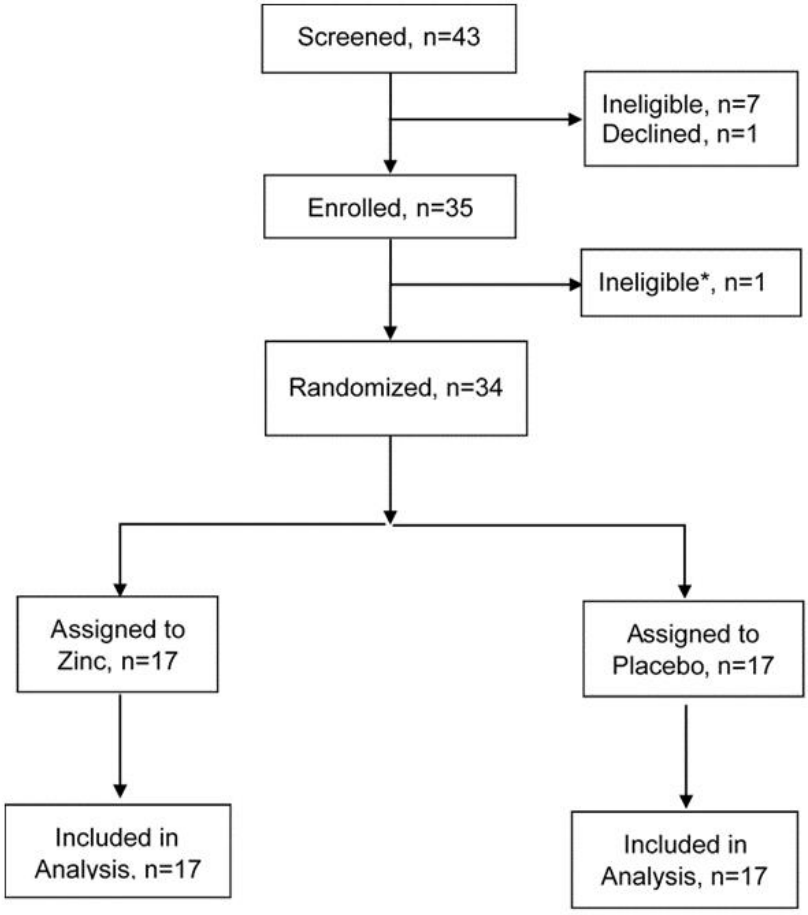
Study Visit Week
Titration
Day 0-3
Day 4-7
Day 8+
50 mg or placebo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Declined, n=1
Enrolled, n=35
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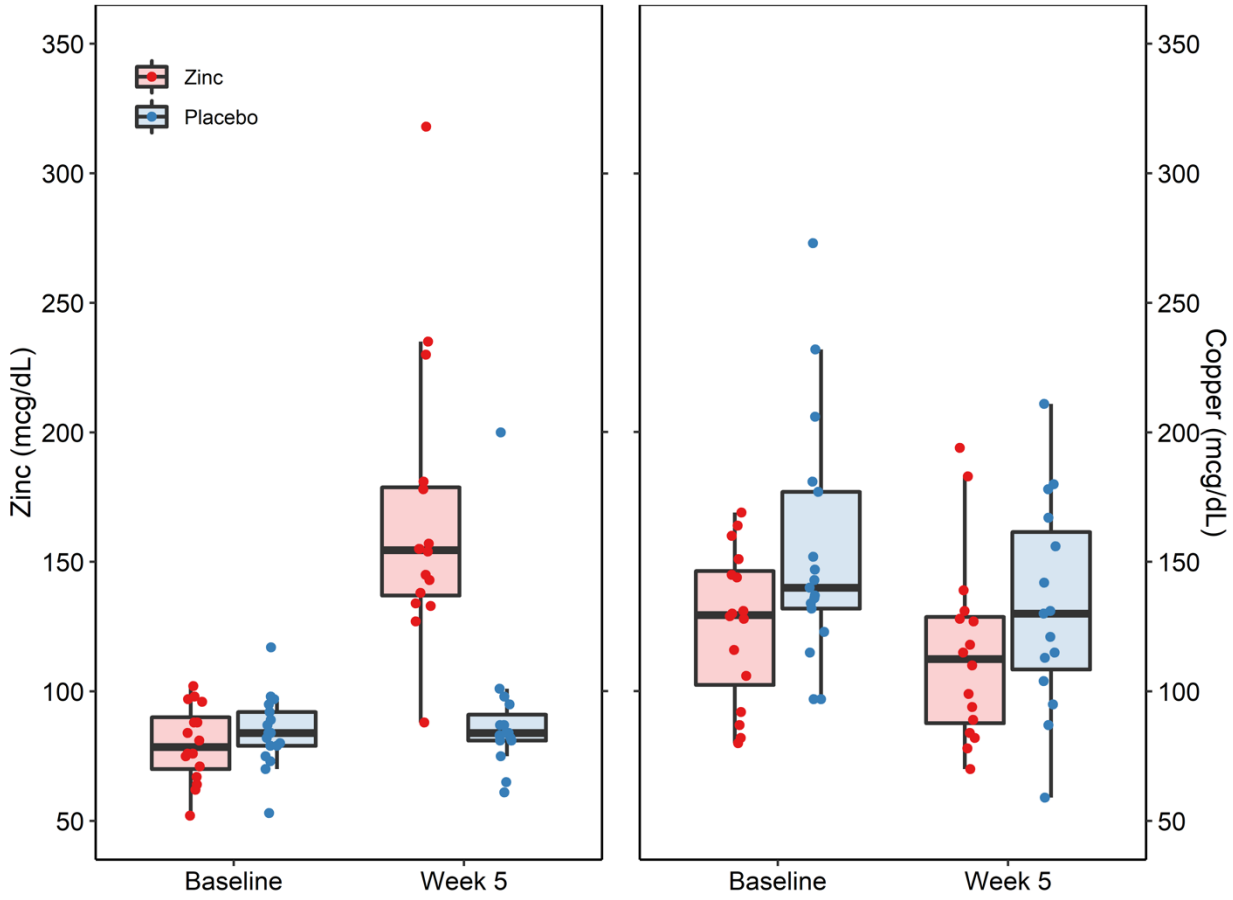
Included in Analysis, n=17


Zinc
Placebo
Zinc (mcg/dL)
Copper (mcg/dL)
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300
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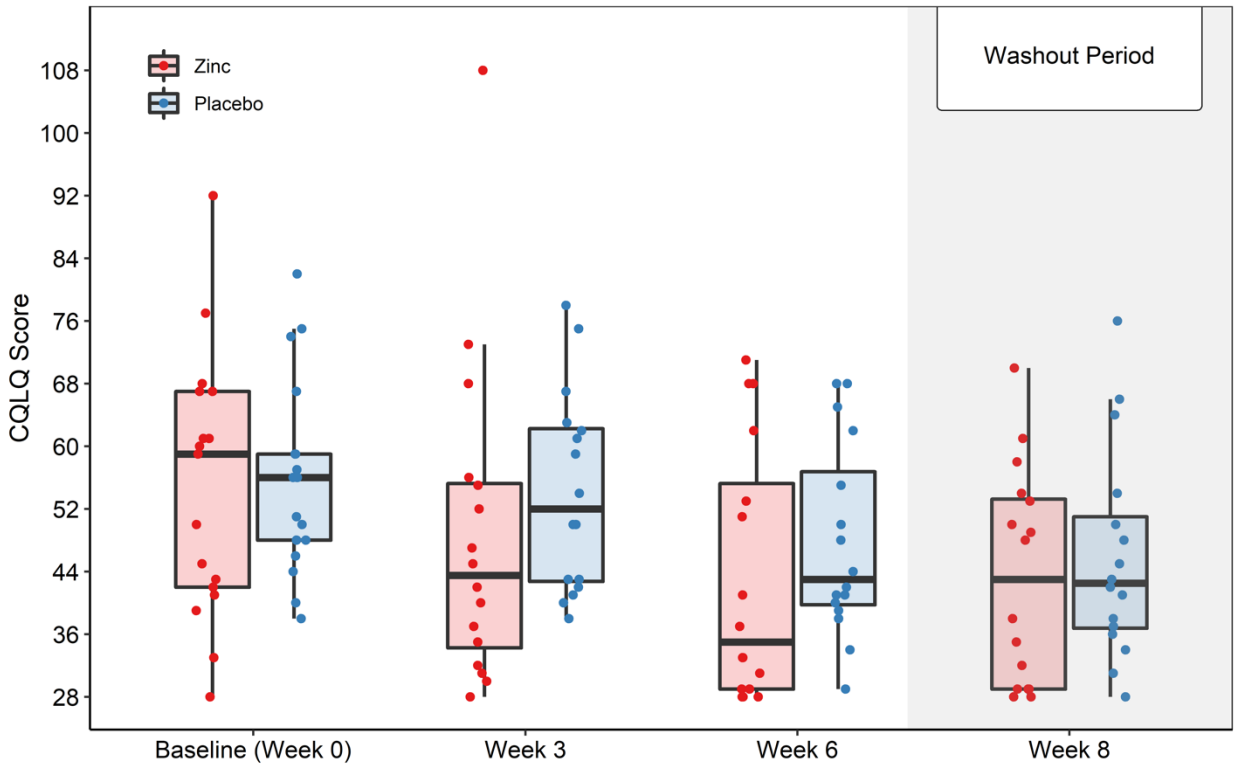
Baseline
Week 5
Baseline
Week 5


Zinc
Placebo
Washout Period
CQLQ Score
108
100
92
84
76
68
60
52
44
36
28
Baseline (Week 0)
Week 3
Week 6
Week 8