European Journal of Respiratory Medicine

2024; 5(1): 409- 415. doi: 10.31488/EJRM.144

Research Article

The Effect of Sodium Pyruvate Nasal Spray on Coughing in Patients with Idiopathic Pulmonary Fibrosis: A Double-Blinded Randomized Placebo-Controlled Phase 3 Clinical Trial

Dr. Alain Martin PhD*[1], Dr. Christopher Lupfer PhD[2]

1.EmphyCorp/Cellular sciences, Inc., Flemington, NJ, USA

2.Department of Biology, Brigham Young University-Idaho, Rexburg, ID, USA

*Corresponding author: Dr. Alain Martin, EmphyCorp/Cellular sciences, Inc., Flemington, NJ, USA, Email: Dr.martin@erols.com

Received: July 7, 2024; Accepted: July 17, 2024; Published: July 31, 2024

Abstract

Background: By definition, Idiopathic Pulmonary Fibrosis is an interstitial lung disease with progressive fibrosis and unknown etiology. It is the most common form of pulmonary fibrosis with nearly 50,000 new cases each year in the USA. With no cure and few treatment options available, the need for new therapies is great. N115 is a sodium pyruvate based nasal spray that has been tested in IPF patients previously in phase I/II trials with promising results. Methods: This was a 21-day double-blinded randomized placebo-controlled phase III trial. 24 saline placebo control patients and 26 N115 treated patients reported baseline coughs per day for one week and then were treated for 21 days while continuing to report daily coughing. Secondary endpoints included examining patients for FEV1, FVC, and FEV1/FVC ratios at baseline and over the course of 21 days. Results: The data from this study demonstrated that coughing episodes per 24 hours were significantly reduced in N115 treated patients by 38.4% on day 14 and by 73.2% on 22 day of the trial, whereas the placebo treated group reduced coughing by 16.1% on day 22 ($p< 0.0001$). This correlated well with increased FEV1/FVC ratio, which were improved by 27.9% on day 22 with N115 treated patients compared to 2.37% for placebo ($p< 0.0001$). No patients withdrew from the trial. No mild, moderate, or serious adverse events occurred. No safety or abnormal changes occurred with any vital signs, blood chemistry or hematology. Conclusions: This randomized placebo controlled double blinded phase 3 trial demonstrated the efficacy of N115 nasal spray to significantly decrease coughing and increase lung functions compared to the saline control.

Keywords: Idiopathic pulmonary fibrosis, pyruvate, coughing

Introduction

Idiopathic pulmonary fibrosis (IPF) belongs to a group of conditions called interstitial lung diseases (also known as ILD), which describes lung diseases that involve inflammation or scarring in the lung. IPF is a chronic progressive lung disorder associated with excessive tissue remodeling, scarring, and fibrosis, which makes the lungs unable to effectively transport oxygen into the bloodstream resulting in decreased forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) values, decreased SaO_2, and a decrease in nitric oxide associated with nasal inflammation that causes congestion and coughing [1-9]. Inflammatory pathways are upregulated in the nasal epithelium in 80% of patients with IPF, which is part of the etiology of the disease that affects all lung functions [10]. Nasal inflammation induces oxidative stress, decreases lung functions including FEV_1 and FVC values, and increases mucus and coughing [11-12]. A decrease in total lung functions and capacity results in hypoxemia, dyspnea, and poor quality of life, especially sleep disorders [1-9]. Blockage of nasal nitric oxide by inflammation reduces the amount of nitric oxide reaching the lungs, as nitric oxide is a bronchodilator, low levels reduce critical lung functions, leading to increased lung and nasal infections, a reduced SaO_2 level, reduced FEV_1 and FVC levels also leading to mouth breathing and coughing. Coughing frequency is high in patients with advanced IPF, with median 24-h cough counts of 226 to 520, depending on the population studied [4-9, 13-14]. In mild to moderate cases in IPF patients, cough counts vary from 4-57 per 24-h. Strikingly, IPF patients experience more cough symptoms during the daytime (median hourly cough rate 14.6 during the day versus 1.9 during the night) [4-9, 13-14]. Chronic cough in IPF is not related to age or gender and is more common in advanced disease and in “never-smokers” [4-9, 13-14].

Current treatments for IPF rely mainly on supportive therapies like O_2 administration. Nasal steroids and over-the-counter

(OTC) nasal treatments are used, but may shut down the synthesis of nasal nitric oxide, which then leads to decreased lung functions and a 34% increase in infections [15-21]. Nintedanib slows the rate of decline for FVC to 52.3% in 24 weeks compared to the non treatment group of a 66.7% decline in FVC [22]. Unfortunately, it has numerous side effects, especially on the liver. Pirfenidone has been shown to improve survival as well as improve FVC but also has significant adverse events [23]. Overall, there is a clear need for additional therapies for IPF.

Sodium pyruvate is a natural metabolite and demonstrated extracellular antioxidant of the human body [24]. It has been shown to significantly reduce inflammatory agents throughout the human body, including the lungs and nasal passages, allowing nasal nitric oxide to reach the lungs to increase bronchodilation, thus increase lung functions and decrease coughing [15-21,25-34]. The safety and efficacy of the 0.2% sodium pyruvate nasal spray in patients with allergic rhinitis, nonallergic rhinitis, COPD, cystic fibrosis, sinusitis, Long COVID, COVID and pulmonary fibrosis, including IPF, were collected from 2,130 over 22 years from the 23 phase 1/2/3 clinical trials. Relevant to this study was the examination of patients with long-COVID [17], which can cause pulmonary fibrosis [35]. In this open label phase II trial, patient baselines were established for the first 7 days, when there was no treatment, and patient data demonstrated little to no change in symptoms including coughing/sneezing, and trouble breathing. However, after the inhalation of the 0.2% sodium pyruvate nasal spray for the next 7 days, patient data demonstrated clinically and statistically significant improvements in both coughing/sneezing and improved breathing [17]. Similarly, a second open label trial with 15 pulmonary fibrosis patients that remained on their current therapies showed that N115 treatment improved lung function as determined by changes in FVC, FEV_1, PEF, and FEV_1/FVC ratios. N115 treatment also reduced coughing in all patients These results indicated that current therapies in use are inadequate alone to treat patient with IPF [17].

The purpose of this clinical trial was to determine the effects of sodium pyruvate nasal spray (N115) to reduce coughing and increase lung functions in IPF patients. This was a phase III, 21-day double-blinded randomized placebo-controlled trial designed to determine if patients with idiopathic pulmonary fibrosis treated with N115 nasal spray solution will reduce the primary endpoint of coughing episodes by 25%. (An episode was defined as 5 or more coughs per hour.) Secondary endpoints included examining the effects of N115 on lung function (FEV1, FVC endpoints of 12% or more) and improved FEV_1/FVC ratios.

Methods

Study design overview

The study goal was to enroll 25 patients (actual enrollment was 26) with confirmed IPF into the trial in the sodium pyruvate (N115) treatment group and 25 with confirmed IPF to be enrolled in the trial in the placebo group (actual enrollment was 24). Efforts were made to include women and minorities. The study was a randomized, double-blinded placebo-controlled trial blinded to both subjects and study investigators. Upon enrollment, each subject was sequentially issued a unique subject number starting at 100. Once a number had been assigned to a subject, it was not re-assigned to another subject. The data from all subjects that were given a study compound was retained for analysis. No patients withdrew from the study. All 50 patients completed all testing.

Prestudy

Individuals with a clinical diagnosis of idiopathic pulmonary fibrosis (as defined by the WHO and the Thoracic Society) were solicited for participation in this phase 3 trial. After signing the informed consent, participants were randomly assigned to either the placebo or drug groups in a double blinded randomized fashion. On pre-study day 1 (Screening Visit), and, after signing the informed consent, they had their FEV_1, and FVC levels recorded (baseline). All subjects had a blood sample taken, and women of child-bearing age provided a urine sample for pregnancy testing. The subjects filled out a quality-of-life questionnaire (chronic respiratory disease questionnaire (CRDQ) and were given a data logbook in which they recorded the number of coughs they experience each day for 7 days until they returned to the clinic to begin the study (baseline). Any subject who was not compliant ≥ 80% was not entered into the trial. All patients complied.

Blood was analyzed for CBCs, and for standard clinical variables, including urea nitrogen, serum creatinine, total protein, serum albumin, total globulin, albumin/globulin ratio, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST or SGOT), Alanine Aminotransferase (ALT or SGPT), Lactate Dehydrogenase (LDH), Gamma-glutamyl Transferase (GGT), Serum Sodium, Potassium and Chloride, Carbon Dioxide, C-reactive protein, and Total Cholesterol:HDL Ratio to determine organ health. Subjects could not enter the study until the blood and urine samples were analyzed and evaluated to confirm that subjects did not have a metabolic abnormality that would prevent entry and that women were not pregnant.

Study days

Following the 7-day pre-study period, eligible IPF patients returned to the clinic and were admitted to the 21-day study. On the first day of the study, these patients had a physical exam, and their vital signs were recorded. Then, their FEV_1 and FVC levels and frequency of coughing were examined. Patients were instructed on how to self-administer their first dose of the nasal spray drug or placebo by first forcefully expelling air from their lungs, and then spraying 3 squirts of the drug into each nostril, and then forcefully inhaling the drug so that the drug is inhaled into the airways. After 1 hour, the subjects had their vital signs, FEV_1 and FVC measurements taken again. Efficacy and safety evaluations occurred at this 1-hour time point, too, and then again at 2 and 3 hours. The subjects filled out the product evaluation questionnaire, were given a daily data log form and were given enough drug to last for 21 days (3 bottles) and released from the clinic.

For the next 21 days, subjects self-administer 3 squirts per nostril of the nasal spray, as instructed, 3 times daily; upon wakening, noon/midday, and before bedtime, Additionally, they filled out the Daily Data Log form each day to record the number of daily coughs. Patients were contacted by phone every 2 days to review symptoms and protocol compliance.

On days 8, 14 and 22, they returned to the clinic and had their

blood analyzed, vital signs taken, and they were tested for FEV_1 and FVC. The number of coughs they experienced and other information was discussed with the clinician. They filled out the product evaluation questionnaire and the CRDQ, and they were released from the study on day 22. These data were then evaluated.

Criteria for patient selection/exclusion of patients

The patient population included adult patients ≥18 years old with mild to moderate IPF with FVC and FEV1 values ≥50% of predicted values. IPF was defined in accordance with the most recent collaborative guidelines from the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association including HRCT scan and/or lung biopsy consistent with unusual interstitial pneumonia (UIP), especially honeycombing, without identifiable cause related to other ILD such as drug toxicity, occupational or environmental exposure or connective tissue disease.

Inclusion criteria

• Individuals with a clinical diagnosis of idiopathic pulmonary fibrosis as determined by clinical evaluation and lung function tests, with a condition-related cough.

• Mild to moderate FEV1 and FVC at 50% or greater of standard

• Individuals who agree to abstain from sexual intercourse or agree to use condoms or vaginal diaphragms or other devices designed to prevent conception, during the entire course of the study.

Exclusion criteria

• Pulmonary disease other than idiopathic pulmonary fibrosis.

• Respiratory infections in the last 2 weeks.

• Clinically significant cardiac disease including uncontrolled congestive heart failure and unstable angina.

• Pregnancy

• Females of childbearing potential age not on adequate contraception or lactating females.

• Subjects less than 18 years of age.

• Hospitalization within the last 6 months due to acute exacerbation of airway disease.

• Subjects with a clinically significant abnormal chest X-ray within past 12 months.

• Medication changes within 1 month of study entry except for antiviral, antibiotic, or antimicrobial medications as well as corticosteroids, antihistamines, or anti-inflammatory medications.

• Subjects who have participated in another drug treatment study within the last month.

• Subjects with a current history of alcohol or recreational drug abuse.

• Subjects who have taken dietary supplements containing pyruvate within 24 hours prior to the screening visit.

Table 1. Demographics for Patients with Idiopathic Pulmonary Fibrosis

Demographics	Age (STDEV)	Sex	Stated Ancestry
Placebo	46.5 (13.9)	(F)12 (M)12	White: 22 Hispanic: 1 Black: 1
Pyruvate	47.5 (12.3)	(F)16 (M)10	White:23 Hispanic: 2 Black: 1

• Subjects with metabolic diseases (diabetes, hypoglycemia, etc.).

Products description

The product is a 20 mM (0.2%, 2.2 mg/mL) sodium pyruvate nasal spray in 0.9% sodium chloride with benzalkonium chloride preservative, pH 7.2 (N115). The placebo control is 0.9% saline and benzalkonium chloride preservative, pH 7.2. Both N115 and saline controls are delivered by a Mistette Mark II (MeadWestvaco, Richmond, VA, USA) nasal spray pump, or similar device, that delivers a 0.1 mL metered dose from a 30 mL polypropylene bottle. The product is sealed in tamper evident plastic and labeled with "Caution: New Drug—Limited by Federal (or United States) law to investigational use." 2 bottles are packaged in a white paperboard box with the expiration date of the product printed on the box. The N115 and placebo are packaged in identical packaging and are indistinguishable from each other to ensure blinding. The product comes with instructions for administration (3 sprays per nostril).

Concomitant therapy

All concomitant medications, both prescribed and over the counter (OTC) (including but not limited to natural food supplements), were recorded in the CRF. Subjects were permitted to continue to use their normal therapy as long as they list it as a current medication, and it is not prohibited by the exclusion criteria. Allowable concomitant therapy includes antiviral, antibiotic, antimicrobial, corticosteroids, antihistamines, or anti-inflammatory medications. The clinician could prescribe "rescue medication" as needed by any of the patients. Patients could continue taking nutritional supplements as long as they did not contain pyruvate. Subjects were not permitted to use any intranasal medications or lavages during the trial or for 1 week before enrollment in the trial.

Study data collection and endpoints

During the screening visit and throughout the study period, observations for safety included a pregnancy test for women of child-bearing age and physical exams included, Vital Signs, Weight, Blood pressure, Pulse, and Temperature. Urea nitrogen and blood analysis with complete blood count (CBC), serum creatinine, total protein, serum albumin, total globulin, albumin/globulin ratio, total bilirubin: alkaline phosphatase: aspartate aminotransferase (AST or SGOT): alanine aminotransferase (ALT or SGPT), LDH, GGT, serum sodium, potassium, chloride, carbon dioxide, total cholesterol, and LDL/HDL ratio. Adverse events were monitored.

Observations for efficacy included evaluation of lung func-

tion, as determined by FEV_1, FVC, and number of daily coughs.

Table 2. Testing Schedule

Test	Screening	Day 1 0,1,2,3 Hours	Day 8	Day 14	Day 22
Clinic Visit	+	+	+	+	+
Informed Consent	+				
Medical History	+				
Physical Exam/	+	+		+	+
Product Eval Q	+			+	+
CDRQ	+		+	+	+
Administer Drug		+	+	+	+
Blood Sample	+			+	+
Vital Signs	+	+	+	+	+
Pregnancy Test for Females	+				
Concurrent Meds Taken	+	+	+	+	+
SaO_2	+	+	+	+	+
Nasal Inflammation	+	+	+	+	+
FEV_1	+	+	+	+	+
FVC	+	+	+	+	+
Coughing Data Logbook*	+	+	+	+	+
Adverse Events			+	+	+
Phase Product Evaluation	+	+	+	+	+

*The coughing data logbook was to be filled out by the patient every day, starting at the pre-study visit through day 21.

Daily data logbook

Subjects used this diary card to record the number of their coughs per day, any self perceived adverse events, and any medication changes during the study.

Results

The purpose of this 21 day clinical trial was to demonstrate the efficacy of sodium pyruvate (N115) to primarily reduce coughing and secondarily increase lung functions (FEV_1, FVC and FEV_1/FVC ratios). The data from this study demonstrated that coughing episodes per 24 hours were significantly reduced in all N115 treated patients, with no exceptions, by day 14 of the trial and by 73.2% on day 22 of the trial; whereas the placebo treated group reduced coughing by only 16% by day 22 of the trial. The difference was highly significant (Day 22, $p<0.0001$) and exceeded our a priori threshold of >25% reduction in coughing (Table 3). This correlated well with a significant improvement in lung function as determined by the FEV_1/FVC ratio, which increased by 27.9% by week three, with N115 treated patients, when compared to placebo that increased the ratios by only 2.73% (p= 0.0001) (Table 4). Patient FEV_1 and FVC numbers were highly variable and only N115 treated patients at week 2 showed a significant 26.6% improvement compared to 6.83% in the placebo group (p=0.0004) (Table 5). Although week 3 showed a similar 26.6% mean improvementy in the N115 treated group, this did not quite achieve statistical significance compared to the 12.5% improvement in the control group (p=0.057) (Table 5). After day 21, patients discontinued use of the study medication. Patients were contacted by phone for follow up after 3 months. Impressively, patients reported reduced coughing for a mean 38.8 days for N115 compared to only 5.54 days for the placebo ($p<0.0001$). Patients on N115 also reported a sustained lower number of coughs per day relative to their baseline coughing (-23.7%) compared to the placebo (-11.9%) (p=0.012) (Table 6). Overall, patients receiving N115 reported that their breathing was better, their coughing was reduced, and they were able to sleep better, thus improving their quality of life.

Safety reports

No patients withdrew from the trial. No mild or moderate or serious adverse events occurred. There were four nose irritations listed in the N115 treatment group and all had an adverse event rating of 1 (unrelated to the drug) as determined by the attending physicians. All occurred in the first week of testing, lasting no more than 2 days and then resolved with no further irritations occurring in the last two weeks. One of those patients also reported a headache in the first week that resolved with the administration of Tylenol. A fifth patient that received saline reported having nausea for two days, that resolved on taking loratadine. That event was listed as a 2 = (unlikely related). One of the four N115 treated patients had nausea for three days in week 2 that also resolved by itself and was rated a 2. No 3-5 adverse events were reported by/for any patients.

Conclusions

As discussed, IPF is a chronic progressive lung disorder associated with excessive tissue remodeling, scarring, and fibrosis, which makes the lungs unable to effectively transport oxygen into the bloodstream resulting in decreased forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) values, decreased SaO_2, and a decrease in nitric oxide

Table 3. The number of coughs per 24 hours was derived by adding all coughs per week and dividing by 7. Statistical analysis was performed by two-way ANOVA with Šídák's multiple comparisons test. Percent change was determined compared to the untreated baseline.

Placebo Coughing (n=24)	**Week 1 untreated**	**Week 2 treated**	**Week 3 Treated**	**Week 4 Treated**	**% Change Week 2**	**% Change Week 3**	**% Change Week 4**
Aver.	**45.5**	**43.9**	**41.3**	**38.2**	**-4.08**	**-9.62**	**-16.1**
STDEV	18.6	18.6	17.7	16.7	5.2	7.9	11.0
Pyruvate Coughing (n=26)	**Week 1 untreated**	**Week 2 treated**	**Week 3 Treated**	**Week 4 Treated**	**% Change Week 2**	**% Change Week 3**	**% Change Week 4**
Aver.	**46.5**	**42.2**	**28.7**	**12.7**	**-10.2**	**-38.4**	**-73.2**
STDEV	21.2	20.0	13.9	6.9	6.4	11.0	8.1
P value	0.99	0.99	0.032	<0.0001	0.016	<0.0001	<0.0001

Table 4. The FEV_1/FVC ratios were determined for each patient over 5 visits on prestudy and study day 1,8,14, and 22. Statistical analysis was performed by two-way ANOVA with Šídák's multiple comparisons test. Percent change was determined compared to the untreated baseline.

Placebo FEV_1/FVC (n=24)	**% Change Visit 2**	**% Change Visit 3**	**% Change Visit 4**	**% Change Visit 5**
Average	1.02	1.29	1.83	2.73
STDEV	4.65	3.48	3.98	5.34
Pyruvate FEV_1/FVC (n=26)	% Change Visit 2	% Change Visit 3	% Change Visit 4	% Change Visit 5
Average	4.28	13.0	18.8	27.9
STDEV	6.14	13.0	15.9	22.0
P value	0.15	0.0005	<0.0001	<0.0001

Table 5. Percentage change in FEV_1 and FVC from baseline as measured on prestudy and study day 8,14, and 22. Statistical analysis was performed by two-way ANOVA with Šídák's multiple comparisons test. Percent change was determined compared to the untreated baseline.

"Placebo FEV_1 and FVC (n=24)"	"FEV_1 % Change Visit 3 "	"FEV_1 % Change Visit 4"	"FEV_1 % Change Visit 5 "	"FVC % Change Visit 3 "	"FVC % Change Visit 4 "	"FVC % Change Visit 5 "
Average	**5.79**	**6.83**	**12.5**	**4.25**	**2.46**	**10**
STDEV	21.7	18	20.3	18.9	13.1	19.8
"Pyruvate FEV_1 and FVC (n=26)"	" FEV1% Change Visit 3 "	"FEV_1 % Change Visit 4"	"FEV_1 % Change Visit 5 "	"FVC % Change Visit 3 "	"FVC % Change Visit 4 "	"FVC % Change Visit 5 "
Average	**17.5**	**26.6**	**26.6**	**8.85**	**12.1**	**8.96**
STDEV	21.8	15.4	20.8	21.6	16.8	21.4
P value	0.18	0.00043	0.057	0.81	0.08	0.99

associated with nasal inflammation that causes congestion and coughing (1-9). Although inflammatory pathways are upregulated in the nasal epithelium in 80% of patients with IPF, steroid and general anti-inflammatory drugs have little effect on the progression of the disease (10). Two drugs (Nintedanib and Pirfenidone) are recommended for use in IPF, although they slow the progression of fibrosis and have some effect on FVC, they also have many side effects [22-23]. Currently, there is no cure other than a lung transplant.

Sodium pyruvate is a natural antioxidant of the human body and as an antioxidant it has been shown to significantly reduce inflammatory agents throughout the human body, including the lungs and nasal passages, allowing nasal nitric oxide to reach the lungs to increase bronchodilation [15-21, 25-34]. In addition to 8 human clinical studies conducted on the effect of nebulized, orally inhaled sodium pyruvate on the lungs, 7 human nasal inhalation clinical studies were conducted previously using a sodium pyruvate nasal spray which showed decreased nasal inflammation, a reduction in inflammatory cytokines, and when measured, demonstrated an increase in lung functions, a decrease in coughing, including in patients with pulmonary fibrosis [15-21]. The concentrations of N115, sodium chloride

Table 6. Long term effects of treatment on coughing. Patients reported the duration of reduced coughing after cessation of treatment and average number of coughs per 24h was compared to the untreated baseline. Statistical analysis was performed by the unpaired t-test.

Placebo Coughing (n=24)	Duration post study (Days)	% Change Coughs per 24h
Average	5.54	-11.9
STDEV	3.97	14.2
Pyruvate Coughing (n=26)	Duration post study (Days)	% Change Coughs per 24h
Average	38.8	-23.7
STDEV	26.6	17.5
P value	p<0.0001	0.012

and preservative in the delivery formula, can vary depending on the route of delivery, nebulized (orally inhaled) or nasal spray which can also depend on the severity of the lung or sinus disease. Globally over 3.5 million patients have been treated in over 200 hospitals, demonstrating the ability of sodium pyruvate nasal spray to reduce nasal inflammation, erythema, and edema, and allow an increased level of nasal nitric oxide to reach the lungs and increase lung functions [15-21]. The data from over 2000 patients treated with 0.2% sodium pyruvate nasal spray with diseases ranging from allergic rhinitis, nonallergic rhinitis, COPD, cystic fibrosis, sinusitis, Long COVID, COVID and pulmonary fibrosis (including IPF) over 22 years from the 23 phase 1/2/3 clinical trials has shown that sodium pyruvate is both safe and effective. In long COVID patients, the inhalation of the 0.2% sodium pyruvate nasal spray demonstrated clinically and statistically significant improvements in headaches ($p = 0.0373$), improvements in coughing/sneezing ($p = 0.0091$) by 60%, and improvements in trouble breathing ($p < 0.0001$) 61%. Fatigue, anxiety, loss of taste/smell, congestion and body aches also showed some improvement [17]. Pharmacodynamic Pharmacokinetics and carcinogenetic studies performed by NIH in 38 human clinical trials, confirmed that hyperpolarized [13C]pyruvate is taken up by all organs including the respiratory system and metabolized to acetate, CO_2 and H_2O and is also converted to lactate or alanine a well-defined biochemical pathways [10,15-21,27,28,30,33,36-37]. It is also secreted by cells, readily enters cells, and can directly react with toxic compounds such as H_2O_2 and peroxynitrites to "detoxify them" [10,15-21,27,28,30,33,36-37]. In genetic toxicology test systems, pyruvate has never been found to mutate DNA, is not genotoxic, mutagenic, or carcinogenic [37].

This Phase 3 clinical trial demonstrated in a well-controlled manner the efficacy of sodium pyruvate (N115) to reduce coughing and increase lung functions. The data from this study demonstrated that coughing episodes per 24 hours were significantly reduced in all N115 treated patients, with no exceptions, by 38.4% on day 14 and by 73.2% on the 22 day of the trial; whereas the placebo treated group reduced coughing by only 16% on day 22. The difference was highly significant ($p= 0.0001$) and achieved the primary endpoint of the study by reducing coughing by more than 25%. The data also demonstrate that N115 can significantly improve FEV_1/FVC ratios and to a lesser extent improve FEV_1 levels alone. In conclusion, N115 is a promising treatment for patients with IPF to both improve quality of life and lung function.

References

1. Lamas DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med. 2011; 184: 842–847.
2. Mermigkis C, et al. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? Sleep Breath. 2010; 14: 387–390.
3. Kilduff CE, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath. 2015; 19: 385–391.
4. Birring SS, et al. Obstructive sleep apnea: a cause of chronic cough. Cough. 2007; 3: 7.
5. Chan KK, et al. Chronic cough in patients with sleep-disordered breathing. Eur Respir J. 2010; 35: 368–372.
6. Chan K, Ing A, Birring SS. Cough in obstructive sleep apnea. Pulm Pharmacol Ther. 2015; 35: 129–131.
7. Boulet LP, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. Chest. 2015; 147: 804–814.
8. Lee KK, et al. A longitudinal assessment of acute cough. Am J Respir Crit Care Med. 2013; 187: 991–997.
9. Lechtzin N, Hilliard ME, and Horton MR. Validation of the cough quality-of-life questionnaire in patients with idiopathic pulmonary fibrosis. Chest 2013; 143: 1745–1749.
10. Xu HN, et al. Differentiating inflamed and normal lungs by the apparent reaction rate constants of lactate dehydrogenase probed by hyperpolarized 13C labeled pyruvate. Home vol 6 Feb 28 2016
11. Lee SY. Influence of Chronic Sinusitis and Nasal Polyp on the Lower Airway of Subjects without lower airway diseases Allergy Asthma Immunol Res. 2014 July;6(4):310-315. Doi.org/ 10.4168/air 2014.4.4.310
12. Beibei Sun, et al. Associations of short-term PM2.5 exposures with nasal oxidative stress, inflammation and lung function impairment and modification by GSTT1-null genotype: A panel study of the retired adults. Environmental Pollution Volume 285, 15 September 2021, 117215
13. Morice AH, Kastelik JA, and Thompson R. Cough challenge in the assessment of cough reflex. Br J Clin Pharmacol 2001; 52: 365–375.
14. Spinou A, Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? J Thorac Dis 2014; 6: Suppl. 7, S728–S734.

15. Reel J, Lupfer C. 2021. Sodium Pyruvate Ameliorates Influenza A Virus Infection In Vivo. Microbiol Res 12: 258-267.

16. Abusalamah H, Reel JM, Lupfer CR. 2020. Pyruvate affects inflammatory responses of macrophages during influenza A virus infection. Virus Res 286: 198088.

17. Lupfer C, et al. Inhalation of sodium pyruvate to reduce the symptoms and severity of respiratory diseases including COVID-19, long COVID and pulmonary fibrosis. Eur j of Respir Med. 2021; 3(3): 229-237. 10.31488 EJRM.121

18. Sheridan J, et al. 1997. Evaluation of antioxidant healing formulations in topical therapy of experimental cutaneous and genital herpes simplex virus infections. Antiviral Res 36: 157-166.

19. Martin A, et al. Inhalation of sodium pyruvate to reduce hypoxemia and dyspnea associated with chronic respiratory diseases- a multi-study retrospective analysis. European journal of respiratory medicine. 2011; 4(1); 258-261. Doi; 10.31488/EJRM.124

20. Votto JJ, et al. 2008. Inhaled sodium pyruvate improved FEV1 and decreased expired breath levels of nitric oxide in patients with chronic obstructive pulmonary disease. J Aerosol Med Pulm Drug Deliv 21: 329-334.

21. Martin A, et al. Inhaled sodium pyruvate reduces oxygen radical and inflammatory cytokines in patients with lung and sinus diseases. European Journal of Respiratory Medicine. 2022; 4(2): 320-326. Doi; 10.31488/EJRM.133

22. Mazzei ME, Richeldi L, Collard HR. Nintedanib in the treatment of idiopathic pulmonary fibrosis. Therapeutic Advances in Respiratory Disease. 2015;9(3):121-129. doi:10.1177/1753465815579365

23. Spagnolo P, et al. Non-steroid agents for idiopathic pulmonary fibrosis. Cochrane Database of Systematic Reviews, 2010; 9:1465-1858

24. Guarino VA, et al. Reaction rate of Pyruvate and Hydrogen Peroxide: Assessing antioxidant Capacity of Pyruvate under Biological Conditions. Scientific Reports 2019; 9:19568

25. Bunton CA. Oxidation of α-Diketones andα-Keto-Acids by Hy¬drogen Peroxide. Nature 1949; 163(4142):444-444.

26. Melzer E, Schmidt HL. Carbon isotope effects on the decarboxyl¬ation of carboxylic acids. Comparison of the lactate oxidase reac¬tion and the degradation of pyruvate by H2O2. Biochem J. 1988; 252(3):913-915.

27. O'Donnell-Tormey J, et al. Secretion of py¬ruvate. An antioxidant defense of mammalian cells. J Exp Med. 1987; 165(2):500-514.

28. Andrae U, Singh J, Ziegler-Skylakakis K. Pyruvate and related al¬pha-ketoacids protect mammalian cells in culture against hydrogen peroxide-induced cytotoxicity. Toxicol Lett. 1985; 28(2-3):93-98.

29. Varma SD, Morris SM. Peroxide damage to the eye lens in vitro prevention by pyruvate. Free Radic Res Commun. 1988; 4(5):283-290.

30. Nath KA, et al. Effect of pyruvate on oxidant injury to isolated and cellular DNA. Kidney Int. 1994; 45(1):166- 176.

31. Brunkhorst R, Mahiout A. Pyruvate neutralizes peritoneal dialy¬sate cytotoxicity: maintained integrity and proliferation of cultured human mesothelial cells. Kidney Int. 1995; 48(1):177-181.

32. Shah SV. Role of reactive oxygen metabolites in experimental glo¬merular disease. Kidney Int. 1989, 35(5):1093-1106.

33. Lehninger. 1981 Biochemistry (12th Edition)

34. Dijkstra U, et al. Friedreich's ataxia: intra¬venous pyruvate load to demonstrate a defect in pyruvate metabo-lism. Neurol. 1984; 34(11):1493-1497.

35. Ojo AS, et al. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020: 6175964.

36. Pourfathi M, et al. Metabolic Imaging of Acute Lung Injury Using Hyperpolarized 13C pyruvate in Rodent lungs. Magnetic Resonance Imaging. Dissertation. University of Pennsylvania, 2019 NIH National Cancer Institute.

37. Hyperpolarized Pyruvate (13C) Injection: Investigator's Brochure, 2023 https://imaging.cancer.gov/programs_resources/cancer-tracer-synthesis-resources/docs/c13_pyruvate_IB_PDF.pdf

To cite this article: Martin A, Lupfer C. The Effect of Sodium Pyruvate Nasal Spray on Coughing in Patients with Idiopathic Pulmonary Fibrosis: A Double-Blinded Randomized Placebo-Controlled Phase 3 Clinical Trial. European Journal of Respiratory Medicine. 2024; 6(1): 409 - 415. doi: 10.31488/EJRM.144.