An Open Label Study of the Efficacy, Safety and Tolerability of NP-120 on Idiopathic Pulmonary Fibrosis and its Associated Cough

Bryan CS[1], Williams MS[1], Kolb M[2], Smith J[3], Veitch E[4], Brown J[5], Blom H[6], Beckert L[7], Chang C[8], Wheatley J[9], Bremner P[10]

1. Algernon Pharmaceuticals, Vancouver, Canada 2. McMaster University, Hamilton, Canada 3. University of Manchester, Manchester, UK 4. Concord Repatriation General Hospital, Concord, Australia 5. Cairns Hospital, Cairns, Australia 6. Vale Medical Practice, Brookvale, Australia 7. The University of Otago, Christchurch, New Zealand 8. Waikato Hospital, Hamilton, New Zealand 9. Westmead Hospital, Westmead, Australia 10. TrialsWest, Spearwood, Australia. *cbryan@algernonpharmaceuticals.com*

Introduction

- Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease characterized by scarring of the lungs.
- 70-85% of patients with IPF are affected by a dry, non-productive cough which is refractory to therapy and can dramatically affect a patient's quality of life. Existing IPF drugs have no effect on cough.
- NP-120 (Ifenprodil), an NMDA receptor antagonist selective for the 2B subunit, displayed similar or better reductions of fibrosis compared to pirfenidone and nintedanib in a mouse bleomycin-challenge model, and superiority to gefapixant (a P2X3 inhibitor approved in Japan for the treatment of chronic cough) in a guinea pig citric acid challenge model.
- NMDA receptors are concentrated in the brain, but are also present on pulmonary tissue as well as neutrophils and macrophages.

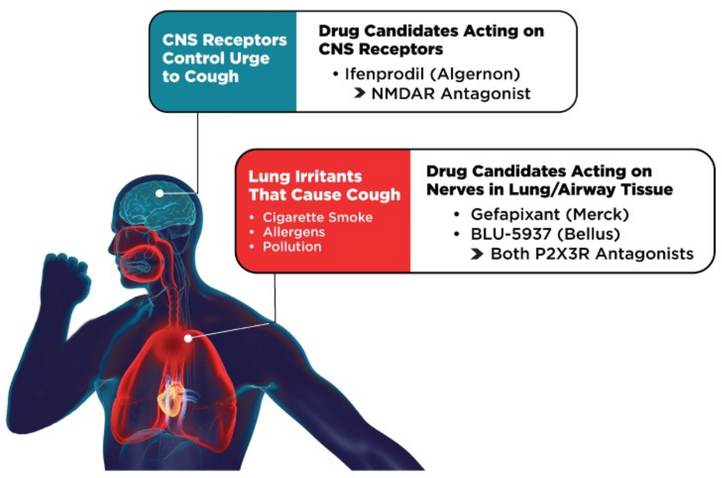

Figure 1. Targets of Drugs for Chronic Cough

Methods

- Algernon ran a 20 patient, single-arm, proof-of-concept study in patients with IPF and cough (NCT04318704).
- Subjects were treated with NP-120 TID for 12 weeks.
- The co-primary endpoint of IPF was the preservation of lung function, measured by the proportion of patients achieving no worsening of their forced vital capacity (FVC). FVC was measured at baseline, then at 12 weeks. A follow-up measurement was taken at 13 weeks.
- The co-primary endpoint for cough was the proportion of patients achieving a 50% reduction over baseline at 12 weeks in cough count, measured by an ambulatory cough monitor (VITALOJAK, Vitalograph, Maids Moreton, UK). Cough counts were also measured at 4 weeks.
- Secondary endpoints included DL_{CO}, patient-reported outcomes of cough severity and quality of life, and biomarkers of fibrosis.
- Safety and tolerability (adverse events) were recorded.

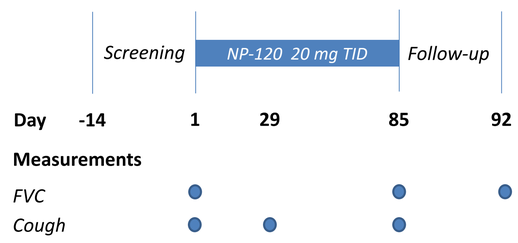

Figure 2. Study Design

Key Inclusion Criteria

- Diagnosis of IPF established during the previous 7 years according to American Thoracic Society/European Respiratory Society/ Fleischner Criteria
- Scored >40 mm on the Cough Severity VAS at screening
- Lung function parameters as follows:
  - FVC >45% of predicted value at screening
  - DLCO (corrected for Hb) of 30% to 79% of the predicted value at screening
- Any existing SOC treatment (pirfenidone or nintedanib) must have been deemed as stable (minimum 3 months) before enrolment

References

1) Nathan SD et al. Eur Respir J 2020; 55:1902151.
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3) Mehta A et al. Chest 2019; 1564S: A1575.
4) Raj AA et al. Handb Exp Pharmacol 2009;(187):311.
5) Lee KK et al. Am J Respir Crit Care Med 2013;187:991.
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7) Organ LA et al. Respir Res 2019 Jul 12;20(1):148

Results

Disposition & Demographics

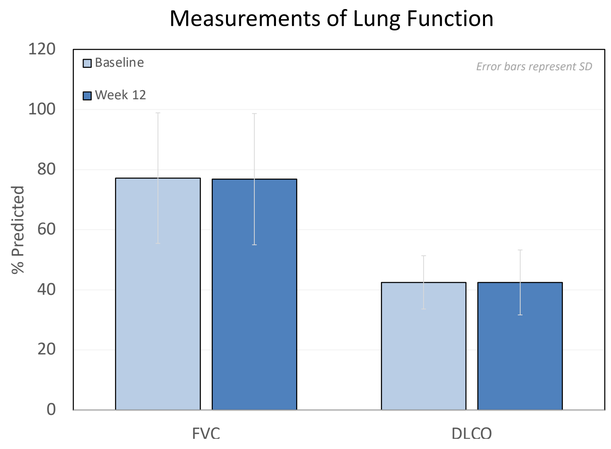
		NP-120 (n=20)
Age, mean (SD)		72.7 (8)
Male, n (%)		14 (70%)
Race, n (%)	White	18 (90.0%)
	Other	2 (10.0%)
BMI (kg/m²), mean (SD)		27.67 (3.10)
SOC, n (%)	Nintedanib	8 (40.0%)
	Pirfenidone	4 (20.0%)
	Both	1 (5.0%)

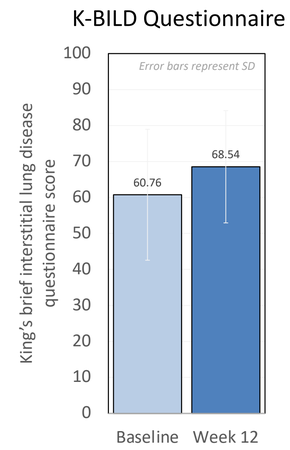
Safety

- The adverse events observed in this trial were consistent with the clinical history of NP-120, established in post-marketing surveillance of over 8,000 patients.
- The majority of AEs were mild or moderate in severity. The most commonly observed treatment related TEAEs in the study were GI disorders (25.0%) and decreased appetite (10.0%).
- Treatment compliance was excellent (>90% for the study).

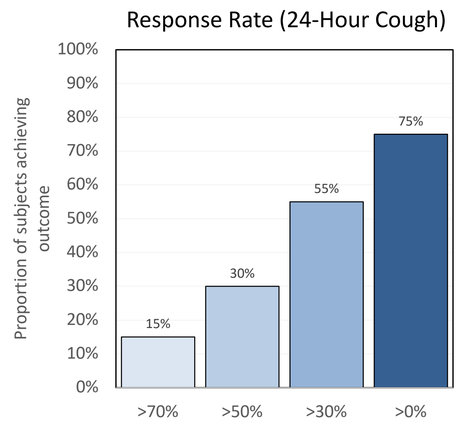
Efficacy in IPF

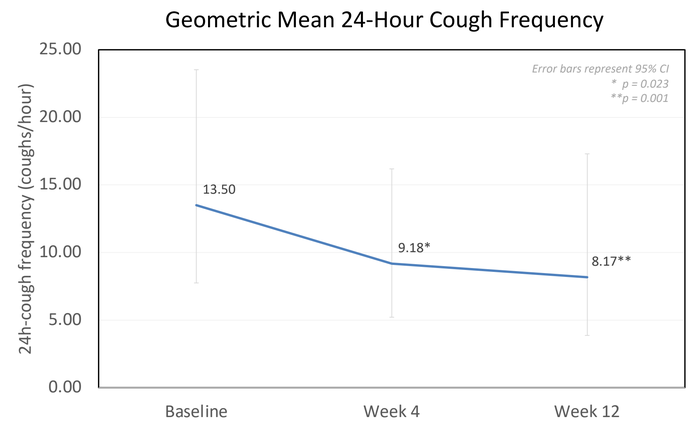
- The co-primary endpoint, the proportion of patients experiencing no worsening of FVC, was 70%. This was significantly better than a hypothesized placebo response of 40%.[1]
- Measurements of FVC and DL_{CO} were unchanged from baseline over 12 weeks, consistent with a preservation of lung function.
- A trend to improvement was observed after twelve weeks of treatments in the King's Brief Interstitial Lung Disease Questionnaire (increase of 7.8 points, p = 0.012). A change of 5 points is thought to be the minimal clinically important difference (MCID).[2]

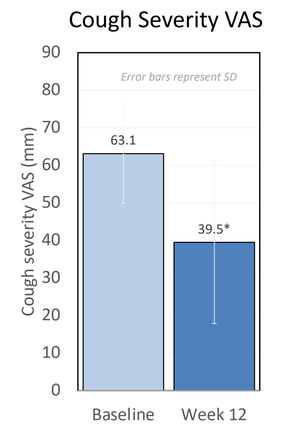


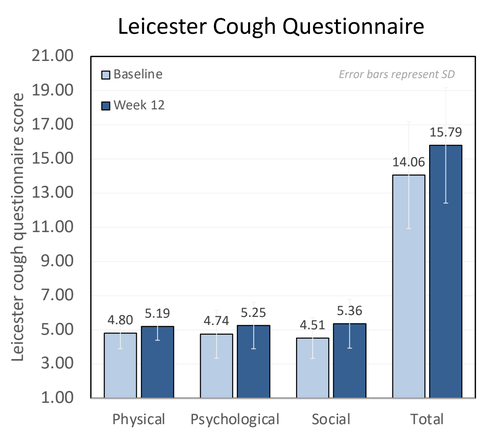


Efficacy in Cough





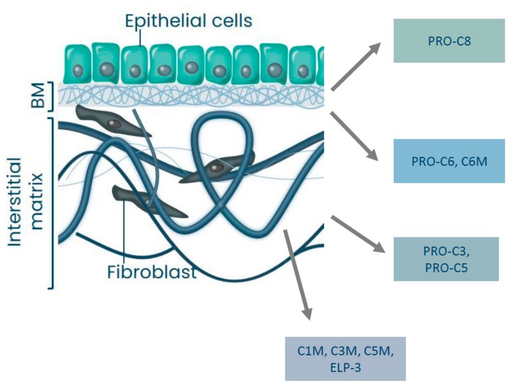




- The co-primary endpoint, the portion of patients achieving at 50% reduction in cough count over baseline was 30%. This was not significantly different from a hypothesized placebo response of 25%.[3]
- The geometric mean 24-hour cough count was reduced by 32.0% after 4 weeks of treatment (p = 0.023) and 39.5% after 12 weeks (p = 0.001). Reductions were similar for waking cough counts (data not shown).
- Scores on the Leicester Cough Questionnaire, a cough-specific quality-of-life scale, were improved by 1.7 points (p = 0.12). The MCIDs are 0.2 (physical), 0.2 (psychological), 0.8 (social) and 1.3 (total).[4]
- The Cough Severity VAS was improved by 37.4% (23.6 mm, p = 0.001). 17 mm is regarded as the MCID in acute cough.[5]

Biomarkers of Fibrosis

- Exploratory biomarkers of tissue remodeling (measures collagen synthesis and degradation) were sampled and measurements were performed at Nordic Biosciences (Herlev, Denmark).[6,7]
- None of the individual markers measured showed statistically significant changes, however, data were only available for 14 subjects. Since existing antifibrotics have negligible effect over these timeframe, the results appear to merit further exploration.



Biomarker	Measures	Baseline (ng/mL)	Week 12 (ng/mL)	Δ	Relative Change (%)	p
PRO-C3	Fibrinogenesis / Fibroblast activity Type III collagen formation	18.116	16.880	-1.236	-6.8	0.34
PRO-C5	Tissue Quality / Collagen fibrillogenesis Type V collagen formation	1615.976	1666.333	50.357	3.1	0.50
PRO-C6	Fibrogenesis / Fibroblast activity / Pro-fibrotic signalling Type VI collagen formation (endotrophin)	11.986	12.407	0.421	3.5	0.37
PRO-C8	Epithelial/endothelial damage Type VIII collagen formation	3.310	2.999	-0.311	-9.4	0.07
C1M	Tissue degradation MMP-degraded type I collagen	62.626	55.833	-6.793	-10.8	0.26
C3M	Tissue degradation MMP-degraded type III collagen	14.824	14.467	-0.357	-2.4	0.36
C5M	Tissue quality / Tissue degradation MMP-degraded type V collagen	14.081	14.360	0.279	2.0	0.64
C6M	Tissue degradation MMP-degraded type VI collagen	35.989	32.560	-3.429	-9.5	0.26
ELP-3	Tissue degradation / neutrophil activity Proteinase 3-degraded elastin	135.640	127.047	-8.593	-6.4	0.16

Conclusions

- NP-120 was found to be safe and well tolerated in IPF patients, and showed efficacy in reducing IPF-associated cough. Measurements of FVC and DL_{CO} were consistent with preservation of lung function.
- Further studies are needed (placebo controlled and properly powered to investigate efficacy and dose effects).

ALGERNON PHARMACEUTICALS