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PEER-REVIEWED
CONFERENCE REPORT



Frailty Prevalent 5 Months Post-COVID-19 Hospitalisation

5-month follow-up of 1,400 people hospitalised for COVID-19 showed that 75% had at least 1 criterion of frailty, even though they were relatively young, working-aged adults.

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MANDALA and DENALI: Albuterol-Budesonide in Asthma

The risk of asthmatic exacerbation was significantly reduced with a fixed-dose of albuterol and budesonide as-needed, as reported in the MANDALA and DENALI trials.

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New Guidelines for IPF and PPF

Updated clinical practice guidelines for idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) were presented, including recommendations for patients with non-IPF interstitial lung diseases.

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COLOPHON

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Letter from the Editor



Dear colleagues,

We would like to invite you to read our summary of the ATS 2022 congress, which was held last May in San Francisco. It was great that we could visit the location physically again. I would like to mention two or three areas of specific interest highlighted in the report.

First, of course, is COVID-19. The SPRINTER study investigated inhaled interferon β in patients who were hospitalised with supplemental oxygen. The primary endpoint of time to hospital discharge was not reached, but in a subgroup of patients over 65 years, with comorbidities and some other characteristics, there was a significant reduction in worsening of the disease, compared to placebo. So, this study certainly stimulates additional research on interferon β , for very specific allocated groups.

Also long COVID is getting more and more attention. In a study on almost 1,400 patients, most of them working, 75% had 1 or more criteria of frailty 5 months after the acute disease episode. Five months is certainly not 1 year, but it indicates there's a lot of disability after an acute SARS-CoV-2 infection.

Regarding asthma, we know that there is a shift in the paradigm indicating that in early and relatively mild asthma, we go further and earlier to ICS-LABA combination. At the ATS, there was a subsequent study looking at uncontrolled moderate to severe asthma, questioning if we should also give rescue medication with ICS-LABA instead of only SABA in these patients. The study found significant improvements in exacerbations, hospitalisations, etc., in favour of ICS-LABA as rescue in comparison to only SABA as rescue. While this must be confirmed in more studies, I'm sure that this will also enter the guidelines quite rapidly.

Worth mentioning are 2 studies on respiratory cough, where P2X3 antagonists have shown attenuated symptoms, which is hopeful for patients, and finally, the guidelines on the medical treatment of interstitial lung disease have been updated again. These were presented at the ATS, and recently published.

I hope that you will find some important new data for your clinical practice and we really hope that you will enjoy reading this ATS summary report.

Thank you very much.

Richard Dekhuijzen

Biography

Prof. P.N. Richard Dekhuijzen is Professor of Pulmonology at the Radboud University Medical Center in Nijmegen, the Netherlands. His specific area of clinical and research interest includes asthma, COPD, and inhalation technology. He studied medicine at VU Amsterdam and completed his training in pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam and in the Academic Hospital Nijmegen. In 1989, he finished his PhD thesis on training of the respiratory muscles in COPD, followed by a PhD thesis on steroid induced myopathy of the diaphragm in 1994 at the Catholic University Leuven (Belgium). He is author/co-author of over 330 peer-reviewed papers and many textbook chapters on respiratory medicine. From 2008-2010, he was Head of the Cardiology Department at Radboudumc. Until 2016, he chaired the Department of Pulmonary Diseases, the Heart-Lung Centre Nijmegen, and the Medical Staff at Radboudumc. He is the scientific chair of the Aerosol Drug Management Improvement Team (ADMIT) and chair of the Dutch Inhalation Technology Working Group. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Conflict of Interest Statement:

In the last 3 years, Richard Dekhuijzen and/or his department received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sandoz, Teva, and Zambon.

COVID-19

SPRINTER: SNG001 still in the running?

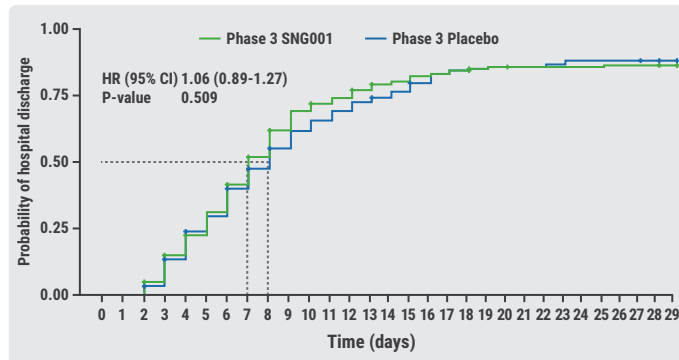
A subanalysis of the SPRINTER trial suggests that inhaled interferon- β (SNG001) may provide a benefit in the prevention of COVID-19 severe disease or death, despite the trial not meeting its primary endpoint. These results provide a potential clinical rationale to continue the investigation of SNG001 in progression and/or mortality in hospitalised patients with COVID-19.

The phase 3, randomised, placebo-controlled, double-blind, SPRINTER study ([NCT04732949](#)) assessed the efficacy and safety of inhaled interferon- β (SNG001) for the treatment of adults hospitalised due to COVID-19 who required treatment with supplemental oxygen by mask or nasal prongs [1]. The rationale behind this trial was based on recent promising phase 2 results [2]. The trial, presented by Dr Philip Monk (Synairgen Research Ltd, UK), randomised 623 patients to receive SNG001 (n=309) or placebo (n=314) on top of standard-of-care [1]. Patients requiring high-flow nasal oxygen therapy, non-invasive ventilation, or endotracheal intubation (invasive ventilation) at randomisation were excluded. Participants self-administered SNG001 once daily as a nebulised dose (15.6 mlU) or placebo for 14 days on top of standard-of-care. The primary endpoint was time to hospital discharge and time to recovery to “no limitation of activities” up to day 28. Key secondary endpoints were progression to severe disease or death within 35 days and progression to intubation.

The primary endpoint was not met; the use of SNG001 did not improve the time to hospital discharge (HR 1.06; 95% CI 0.89–1.27; P=0.509, see Figure). None of the key secondary endpoints pointed to a significant difference either. However, in subgroup analyses, there was an encouraging signal in the reduction in the relative risk of progression to severe disease or death within 35 days (25.7% reduction in the intention-to-treat population and 36.3% reduction in the per-protocol population).

Dr Monk explained that the investigators further enriched for a responder population and focused on the secondary endpoint of progression to severe disease or death. To assess the strength of this signal and identify specific patient populations that might benefit most from treatment, subgroup analyses were performed on groups of patients

Figure: Primary endpoint of SPRINTER: time to hospital discharge [1]



recognised to be at greater risk of developing severe disease in hospital. These analyses included patients ≥ 65 years old, those with comorbidities associated with worse COVID-19 outcomes, and those who, at baseline, despite receiving low-flow oxygen, had clinical signs of compromised respiratory function (defined as oxygen saturation of $\leq 92\%$ or respiratory rate ≥ 21 breaths/min). In this latter group, data showed a 70% drop in patients taking SNG001 progressing to severe disease versus the control group (P=0.046). This was not observed in the overall intention-to-treat population, although there was a trend to reduced progression by 26% in patients treated with SNG001 versus placebo (P=0.161).

SNG001 was well tolerated in the SPRINTER trial, with a favourable safety profile consistent with previous studies. The proportion of participants with any treatment-emergent adverse events was 22.6% in the group receiving SNG001 versus 25.4% in the placebo arm. Likewise, the proportion of participants with any serious treatment-emergent adverse event was 12.6% in the investigational arm and 18.2% in the placebo arm. The serious adverse events most often reported were infections/infestations and respiratory, thoracic, and mediastinal disorders.

In conclusion, while the primary efficacy endpoint was not met, there were trends in favour of SNG001 in the prevention of COVID-19 progression to severe disease or death. Subgroup analyses supported a mild benefit.

1. Monk P, et al. SPRINTER: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Determine the Efficacy and Safety of Inhaled Interferon Beta-1a (SNG001) for the Treatment of Patients Hospitalized Due to COVID-19. Session B12, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Monk PD, et al. Lancet Respir Med. 2021 Feb;9\(2\):196–206.](#)

Nebulised aviptadil “futile” in I-SPY COVID-19 trial

New findings from a phase 2 trial of nebulised aviptadil in critically ill COVID-19 patients showed no benefit of adding this medication to dexamethasone and remdesivir backbone therapy.

The phase 2, open-label, adaptive platform I-SPY COVID-19 Trial ([NCT04488081](#)), which was testing, among other compounds, the nebulised form of aviptadil in critically ill COVID-19 patients, has been prematurely stopped. The trial was designed to rapidly screen potential agents that could substantially reduce the time to recovery (defined as a reduction in oxygen demand) by approximately 50% or risk of mortality in these patients. Prof. Carolyn Calfee (University of California at San Francisco, CA, USA) explained that aviptadil is a synthetic form of a human vasoactive intestinal polypeptide (VIP) and was selected because of the potential to reduce inflammation in COVID-19 patients hospitalised for acute respiratory distress syndrome (ARDS), which is the major cause of death in those critically ill from COVID-19 [1]. The intravenous form of aviptadil is currently being tested in the ACTIV-3b phase 3 trial ([NCT04843761](#)). The nebulised form of aviptadil to be inhaled through a mouthpiece was selected for inclusion in the I-SPY COVID-19 Trial to determine whether nebulised delivery would be effective in speeding recovery from and/or preventing death from COVID-19-related ARDS.

The study enrolled 118 COVID-19 patients on high flow nasal cannula (COVID scale 5; n=103), mechanical ventilation (COVID scale 6; n=8), or mechanical ventilation with additional organ failure (COVID scale 7; n=6), who were randomised to either receive nebulised aviptadil (n=51; 100 µg of nebulised aviptadil inhaled as an aerosol mist 3x per day for up to 14 days) or to a control group (n=67). All patients received dexamethasone and remdesivir as backbone therapy.

The Data Monitoring Committee recommended stopping enrolment to the aviptadil arm early because the agent met the pre-defined futility criterion, which was set in the I-SPY COVID-19 Trial for when there was a >90% probability that the hazard ratio would be under 1.5 when compared with standard treatment ($\text{Pr}(\text{HR} < 1.5) \geq 0.9$), and when there was a 50% probability for achieving a hazard ratio for mortality of <1.0 ($\text{Pr}(\text{HR}_m < 1.0) < 0.5$). The data from nebulised aviptadil patients was compared with that from 67 patients concurrently randomised to the control arm. After all

participants had reached 28 days of follow-up, the results suggested a low probability that the addition of this dose of nebulised aviptadil to backbone therapy via mouthpiece administration would improve outcomes in this population; in fact, the data collected until the time of stopping the trial favoured the control arm (HR 0.56; 95% CI 0.34–0.89).

Prof. Calfee speculated that the negative results may be attributed to the difficulty of effectively delivering nebulised medications via mouthpiece to critically ill patients who are on high flow oxygen (≥ 6 litres) or nebulised into the breathing circuit for mechanically ventilated patients. Factors including high oxygen flow rates, rapid breathing, and mechanical ventilation may have reduced the nebulised medication delivery. Accordingly, nebulised administration of aviptadil at the dose used at flow rates above 6 L per minute is not appropriate in this patient population.

1. Calfee C, et al. The I-SPY COVID Trial: First Results from an Adaptive Platform Phase 2 Trial for Severe COVID-19. Session D94, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Lung transplantation after COVID-19-associated ARDS

The results of a first, international case series indicated that when lung transplantation is the only option for survival in patients with severe, unresolving, COVID-19-associated acute respiratory distress syndrome (ARDS), the procedure can be done successfully, with good early post-transplantation outcomes, in carefully selected patients.

Prof. G.R. Scott Budinger (Northwestern University, IL, USA) presented current data concerning COVID-19 patients at imminent risk of dying due to ARDS who had received lung transplantations [1–4]. He started by saying that “patients with COVID-19-associated ARDS who received lung transplants had similar outcomes compared with transplant patients without COVID-19, despite modestly increased early post-op complications.”

In the retrospective study, Prof. Budinger mostly focused on the case series including 102 patients who underwent a lung transplant at Northwestern Memorial Hospital between January 2020 and September 2021, including 30 patients who had COVID-19-associated ARDS [3]. While rates of transplant complications and length of stays in intensive care units were both higher in the group with COVID-19, patient survival in both groups was not significantly different. Overall, this data was very similar to that of the other studies [2,4].

Prof. Budinger pointed out that this finding is encouraging for the treatment of patients with COVID-19 who have no other options. Furthermore, the collective data can reassure the community that precious resources such as donor lungs will not necessarily have poorer outcomes in candidates with COVID-19.

1. Budinger GS, et al. Lung Transplantation for COVID-19-Associated ARDS. Session A2, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Bharat A, et al. Lancet Respir Med. 2021;9\(5\):487–497.](#)
3. [Kurihara C, et al. JAMA. 2022;327\(7\):652–661.](#)
4. [Roach A, et al. N Engl J Med 2022;386\(12\):1187–1188.](#)

COVI-PRONE trial on its back

The randomised COVI-PRONE clinical trial demonstrated no difference in the risk of endotracheal intubation requirement at 30 days between awake prone positioning and standard positioning for patients with COVID-19 who suffered from acute hypoxemic respiratory failure.

The COVI-PRONE study ([NCT04350723](#)) sought to determine the efficacy and adverse events of awake prone positioning in adults with hypoxemic respiratory failure from COVID-19 [1,2]. It was a randomised, unblinded, parallel-group stratified clinical trial aiming to examine whether awake prone positioning in COVID-19 patients with hypoxemic respiratory failure reduced the risk of endotracheal requirement and mortality. The rationale for this trial lies in previous studies suggesting that the prone position reduces the risk of mortality in COVID-19 patients undergoing invasive mechanical ventilation for acute respiratory distress, but it is not known whether awake prone positioning can prevent intubation or improve survival. “It is also not entirely known if awake prone positioning can actually cause harm due to delayed intubation,” said Prof. Waleed Alhazzani (McMaster University, Canada) [1].

COVI-PRONE was conducted at 21 hospitals and included adults who required at least 40% oxygen or non-invasive positive pressure ventilation and had not received invasive mechanical ventilation. Participants (n=400) were randomised to either the intervention group (n=205; prone position 8–10 hours per day) or the control group (n=195; no prone positioning). Baseline characteristics between the groups were similar in the use of pharmacological agents, such as steroids, antivirals, anticoagulants, or immunomodulators. The primary outcome was endotracheal intubation within 30 days of randomisation.

The results showed that the risk of endotracheal intubation did not significantly differ between groups at 30 days, with the prone group at 34.1% and the control group at 40.5% (HR 0.81;

95% 0.59–1.12; not significant). Similarly, the risk of mortality at 60 days was similar between groups (HR 0.93; 95% CI 0.62–1.40; not significant). No serious adverse events occurred in both groups, though the prone positioning group reported more overall adverse events (26 vs 0), mainly consisting of pain or discomfort attributable to the prone position.

The authors concluded that this trial provided robust evidence that awake prone positioning does not decrease the risk of endotracheal intubation or mortality in patients with acute hypoxemic respiratory failure due to COVID-19.

1. Alhazzani W, et al. COVI-PRONE trial. Session A84, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Alhazzani W, et al. JAMA. 2022;327\(21\):2104–2113.](#)

Mesenchymal stem cells offer no benefit in COVID-19

Although safe, administration of umbilical mesenchymal stem cells (MSCs) did not mitigate acute respiratory distress syndrome (ARDS) in COVID-19 patients in the REALIST-COVID study.

The phase 2 REALIST-COVID trial ([NCT03042143](#)) investigated an off-the-shelf product called ORBCEL-C, which consists of cryopreserved, allogeneic, human umbilical cord tissue-derived CD362-enriched MSCs, for the treatment of COVID-19-related ARDS. A total of 59 patients were randomised to receive 400 million ORBCEL-C MSCs (n=30) or Plasmalyte148 placebo (n=29). Dr Ellen Gorman (Queen’s University Belfast, UK) presented the data [1].

The primary efficacy endpoint, oxygenation index at day 7, was not met. The oxygenation level in the intervention arm (98.3) was similar to that in the placebo arm (96.6; mean difference 1.8; 95% CI -30.7 to 34.3; P=0.92). There was no difference over 14 days either. Likewise, both pulmonary and non-pulmonary function was identical across the groups. Safety data showed no significant differences in the number or severity of adverse events across the groups.

Dr Gorman concluded that although intravenous infusion of 400 million ORBCEL-C MSCs was safe in patients with moderate-to-severe ARDS due to COVID-19, there was no identified improvement in surrogates of pulmonary function in those patients.

1. Gorman E, et al. Repair of Acute Respiratory Distress Syndrome in COVID-19 by Stromal Cell Administration (REALIST-COVID) Phase 2 Randomised Controlled Trial. Session D94, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

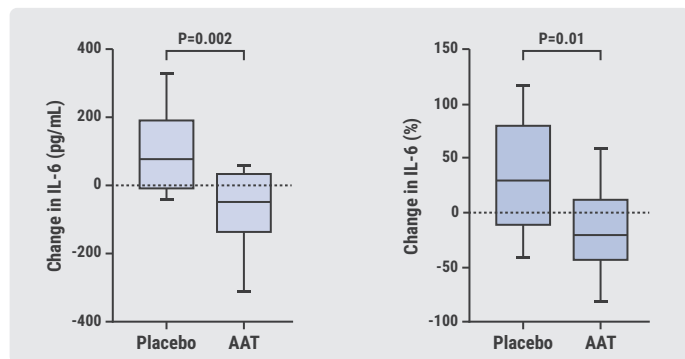
Alpha-1 antitrypsin for ARDS secondary to severe COVID-19

The results of a randomised, phase 2 trial of intravenous, plasma-purified alpha-1 antitrypsin (AAT) for moderate-to-severe acute respiratory distress syndrome (ARDS) secondary to COVID-19 indicated that the treatment is safe and biochemically effective.

A phase 2, randomised, multicentre, randomised, double-blind, placebo-controlled study (EudraCT 2020-001391-15) investigated the use of anti-inflammatory protein AAT purified from the blood of healthy donors as a therapeutic option for patients with severe COVID-19, particularly those who progressed to ARDS (n=36). Dr Oliver McElvaney (Royal College of Surgeons, Ireland) presented the results, which were also recently published in the journal *Med* [1,2].

The results showed that treatment with intravenous AAT resulted in decreased inflammation at 1 week, was safe and well tolerated, and did not interfere with patients' ability to generate their own protective response to COVID-19. The study met its primary endpoint, with decreased circulating IL-6 concentrations at 1 week in the treatment group, as opposed to an IL-6 increase in the placebo group (see Figure). Similarly, plasma sTNFR1 was substantially decreased in the treatment group while remaining unchanged in patients in the placebo arm. AAT did not reduce levels of IL-1 β , IL-8, and IL-10. No difference in mortality or ventilator-free days was observed between groups, although a trend toward decreased time on a ventilator was observed in AAT-treated patients.

Figure: Circulating IL-6 levels were significantly reduced in patients treated with AAT [1]



AAT, alpha-1 antitrypsin.

Based on these results, the researchers suggested that a phase 3 trial is warranted to assess the efficacy and safety of intravenous AAT for patients with ARDS secondary to severe COVID-19.

1. McElvaney O, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Alpha-1 Antitrypsin for ARDS Secondary to Severe COVID-19. Session D94, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [McElvaney OJ, et al. *Med \(N Y\)*. 2022;3\(4\):233–248.](#)

Frailty prevalent 5 months following hospitalisation for COVID-19

A study following nearly 1,400 people who were hospitalised for COVID-19 for up to 5 months after discharge drew some concerning conclusions about the prevalence and progression of frailty among these patients. In total, 75% of the patients had at least 1 criterion of frailty, even though they were relatively young, working-aged adults.

Although frailty is a known risk factor for severe acute COVID-19, including death, as well as being a marker of increased risk for adverse outcomes, it remains unknown what the burden of frailty among COVID-19 survivors is and whether it contributes to long-COVID or post-disease sequelae. The Post-Hospitalisation COVID-19 study (PHOSP-COVID; [ISRCTN10980107](#)) aimed to investigate this association [1]. Interim data were recently published in *The Lancet Respiratory Medicine* [2].

PHOSP-COVID examined 1,399 patients 5 months post-discharge for COVID-19 and tested them for Fried's frailty phenotype [1]. Frailty by the Fried's frailty phenotypes scores inactivity, weight loss, weakness, slowness, and exhaustion to form a composite score. Multivariable logistic regression was performed for the primary outcome of patient-perceived recovery, with the covariates age, sex, ethnicity, BMI, comorbidities, and severity of acute illness. Dr Hamish McAuley (University of Leicester, UK) presented the preliminary data.

At 5 months post-discharge, 22% (n=305) met none of Fried's criteria and were considered not frail; 63% (n=879) fell into the 'pre-frail' category, meeting 1 or 2 of the criteria; and 15% (n=215) met at least 3 criteria. Significant risk factors for frailty were age at admission (P<0.001), the presence of comorbidities, and whether the patient had been working before COVID-19 illness. BMI was not a risk factor in this cohort.

In summary, 75% of adults were pre-frail or frail at 5 months post-hospitalisation for COVID-19, and this included a working-age population. Most (84%) had been working before they had COVID-19. Pre-frailty and frailty are associated with worse symptoms and reduced exercise tolerance and

function, whereas frail individuals appear to have a greater decrease in quality of life and are less likely to feel recovered.

1. McAuley H, et al. Frailty and Physical Performance in 1,133 Patients Five Months Following Hospitalisation for COVID-19. Session C16, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. Evans RA et al. [Lancet Respir Med. 2021;9\(11\):1275–1287.](#)

Paediatric long COVID lacks definitions

An international collaboration has formed the first study to describe the organisation of paediatric long-COVID care. Although paediatric long COVID is recognised worldwide as a multisystemic disease, definitions and care programmes vary between cohorts. A clear definition of paediatric long-COVID is needed to improve international scientific collaboration and patient care.

The lack of scientific guidance in treating children with paediatric post-COVID condition (PPCC) has been problematic. Ms Nadia Baalbaki (Emma Children's Hospital, the Netherlands) presented IP4C, an international collaboration of researchers, patient representatives, and physicians [1]. This study aimed to assess the currently available paediatric, international, long-COVID care programmes and compare the characteristics of their patient cohorts. A cross-sectional analysis from aggregated data collected by a survey explored

topics such as the used definition for paediatric long COVID, the organisation of paediatric long-COVID clinics, and PPCC patients' characteristics.

The study analysed aggregated data from long-COVID patients (n=431) from 17 cohorts in 13 different countries. The mean age of patients ranged from 6.5–16.4 years. Most patients (>90%) had asymptomatic or mild acute COVID-19. Frequent long-COVID symptoms were fatigue, headaches, concentration difficulties, dyspnoea, and sleep disturbances. At least two-thirds of patients were symptomatic for more than 12 weeks (66.6–100%), and 5–37% of patients had severe limitations in daily life. Definitions for long-COVID varied primarily in duration of symptoms and the necessity of microbiologically-proven SARS-CoV-2 infection.

Most long-COVID care programmes consisted of real-life visits with multidisciplinary teams, including general paediatricians, paediatric lung specialists, cardiologists, infectiologists, physiotherapists, and psychologists. Medical investigations revealed substantial disparities in care between the programmes (e.g. spirometry performed in 0–100% of patients).

1. Brackel C, et al. Uniting Global Efforts on Pediatric Long-COVID: Results of the International Post-COVID Condition in Children Collaboration (IP4C). Poster 601, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Asthma Clinical Trial Updates

MANDALA and DENALI pattern success for albuterol-budesonide in asthma

In patients with uncontrolled moderate-to-severe asthma, the risk of asthmatic exacerbation was significantly reduced when patients used a fixed-dose inhaler with a combination of albuterol and budesonide as-needed compared with the use of an inhaler with albuterol alone as-needed, in a dose-dependent manner. A second clinical trial confirmed that both components contributed to albuterol/budesonide efficacy, with the combinations demonstrating superior effects on lung function.

Short-acting β_2 -agonists provide quick asthma symptom relief but fail to address underlying inflammation. Combining short-acting β_2 -agonist albuterol (180 μg) and corticosteroid

budesonide (160 μg) in a single, as-needed, rescue inhaler for asthma could provide rapid bronchodilation while treating airway inflammation. The phase 3, double-blind, randomised, event-driven MANDALA trial ([NCT03769090](#)) looked at patients with uncontrolled moderate-to-severe asthma and asked whether this fixed-dose rescue inhaler could lower the risk for severe asthma exacerbations compared with albuterol monotherapy used as a rescue inhaler. Prof. Alberto Papi (University of Ferrara, Italy) presented the results, which were simultaneously published in the *New England Journal of Medicine* [1,2].

MANDALA enrolled patients with moderate-to-severe asthma of >3 years old who had had ≥ 1 severe exacerbation in the prior 12 months. Despite allowing children, only 183 of 3,132

randomised participants were paediatric patients; the mean age of the intention-to-treat population was 49 years. Participants were allocated to 1 of 3 arms: an arm receiving the combination with a high-dose of budesonide (albuterol 180 µg/budesonide 160 µg), a lower-dose arm (albuterol 180 µg/budesonide 80 µg), or albuterol 180 µg alone. Study medication was administered through blinded, pressurised metered-dose inhalers. All patients continued receiving maintenance inhaled corticosteroids either with or without other medications for their asthma.

The primary endpoint was time to first severe asthma exacerbation, which reported a 27% reduction among participants assigned a fixed-dose combination of the higher dose combination compared with albuterol 180 µg alone (HR 0.73; 95% CI 0.61–0.88; P<0.001). Similarly, a 17% reduction was observed with the lower-dose combination arm (HR 0.83; 95% CI 0.7–0.99; P=0.041), but the data did suggest a dose-response. In an additional intention-to-treat analysis, risk was reduced by 26% with the higher-dose combination (HR 0.74; 95% CI 0.62–0.89; P=0.001) and 16% with the lower-dose combination (HR 0.84; 95% CI 0.71–1.0; P=0.052).

With regard to safety, the incidence of any adverse event was nearly identical across all 3 groups, with 46.2% in the higher-dose combination group, 47.1% in the lower-dose combination group, and 46.4% in the albuterol-only group. Similarly, serious adverse events occurred in 5.2%, 3.8%, and 4.5%, respectively. Adverse events were consistent with the known safety profiles of the individual components; the most common adverse events were nasopharyngitis, headache, and upper respiratory tract infection.

In another session, Dr Bradley Chipps (Capital Allergy & Respiratory Disease Center, CA, USA) presented the results of the phase 3 DENALI trial ([NCT03847896](https://clinicaltrials.gov/ct2/show/study/NCT03847896)) [3]. DENALI was a randomised, double-blind, placebo-controlled, multicentre, parallel-group trial. Similar to MANDALA, it evaluated the efficacy and safety of albuterol/budesonide in a single inhaler but compared it with albuterol and budesonide monotherapy in patients with mild-to-moderate asthma (excluding children aged 4–11 years). Participants (n=1,001) were randomised to 5 treatment groups in a 1:1:1:1:1 ratio: albuterol/budesonide 180/160 µg 4 times daily, albuterol/budesonide 180/80 µg 4 times daily, albuterol alone 180 µg 4 times daily, budesonide 160 µg 4 times daily, or placebo 4 times daily. The trial started with 2–4 weeks of baseline screening, 12 weeks of treatment, and included an additional 2 weeks of follow-up.

The 2 primary efficacy endpoints were designed to gauge the effect of the individual components: (1) the change from baseline in forced expiratory volume in one second (FEV₁) area under the curve 0–6 hours over 12 weeks of albuterol/budesonide treatment compared with budesonide monotherapy to assess the effect of albuterol, and (2) change from baseline in trough FEV₁ at week 12 of albuterol/budesonide compared with albuterol monotherapy to assess the effect of budesonide. Secondary endpoints included the time to onset and duration of response, number of patients who achieved a clinically meaningful benefit in asthma control at week 12, and trough FEV₁ at week 1.

DENALI met its dual primary endpoints. The researchers reported a statistically significant improvement for combined albuterol/budesonide in FEV₁ at week 12 compared with budesonide (least-squares mean [LSM] difference 80.7 mL; 95% CI 28.4–132.9; P=0.003), as well as versus albuterol (LSM difference 132.8 mL; 95% CI 63.6–201.9 and 120.8 mL; 95% CI 51.5–190.1, for 80 and 160 µg budesonide, respectively; both P<0.001). The onset of action and duration of effect were similar on day 1. The safety profiles for both albuterol/budesonide doses were similar to those of each of the individual components.

“Given the efficacy of adding budesonide to albuterol as a rescue medication and the duration of the treatment, we believe that this is going to be a potential change in the paradigm of the use of rescue medication,” Prof. Papi concluded.

1. Papi A, et al. Efficacy and safety of as-needed albuterol/budesonide versus as-needed albuterol in adults, adolescents and children aged ≥4 years with moderate-to-severe asthma: Results of the MANDALA study. Session B12, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Papi A, et al. N Engl J Med 2022; May 15. DOI: 10.1056/NEJMoa2203163.](https://doi.org/10.1056/NEJMoa2203163)
3. Chipps BE, et al. Efficacy and safety of albuterol/budesonide (PT027) in mild-to-moderate asthma: Results of the DENALI study. Session B93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

ACOUSTICS data sounds good for adolescent asthma exacerbations

According to the findings from the terminated ACOUSTICS study, lebrikizumab reduced exacerbations in adolescents with uncontrolled asthma in a dose-dependent manner. The effect was greatest in patients with eosinophils ≥300 cells/microliter.

The phase 3, multicentre, randomised, double-blind, placebo-controlled ACOUSTICS study ([NCT01875003](https://clinicaltrials.gov/ct2/show/study/NCT01875003)) aimed to test the efficacy and safety of lebrikizumab, a high-affinity IgG4

monoclonal antibody targeting IL-13, selectively preventing the formation of the IL-13/IL-4 heterodimer receptor signalling complex. The trial was stopped early by the sponsor.

In ACOUSTICS, participants (n=346 adolescents, aged 12 to 17 years) with uncontrolled asthma – despite using inhaled corticosteroids daily in addition to at least 1 other asthma controller medication – were randomised to receive lebrikizumab 125 mg (n=116) or 37.5 mg (n=113), or placebo (n=117) subcutaneously once every 4 weeks. The primary outcome was the asthma exacerbation rate, defined as new or worsened asthma symptoms that led to treatment with systemic corticosteroids or hospital admission. The time to first asthma exacerbation and safety outcomes were also evaluated. Prof. Stanley Szeffler (Children’s Hospital Colorado, CO, USA) presented the results from the 224 (65%) adolescents who have completed 52 weeks thus far [1].

Compared with the placebo group, participants assigned lebrikizumab 125 mg had a 51% reduction in exacerbation rates (adjusted RR 0.49; 95% CI 0.28–0.83), and the 37.5 mg arm had a 40% reduction (aRR 0.60; 95% CI 0.35–1.03). Compared with the placebo group, patients in the lebrikizumab arms experienced a longer interval before their first asthma exacerbation for both the 37.5 mg dose (HR 0.40; 95% CI 0.22–0.73) and the 125 mg dose (HR 0.37; 95% CI 0.21–0.66).

The baseline median blood eosinophil count was 295 cells/ μ L; the researchers accordingly looked at the data using a threshold

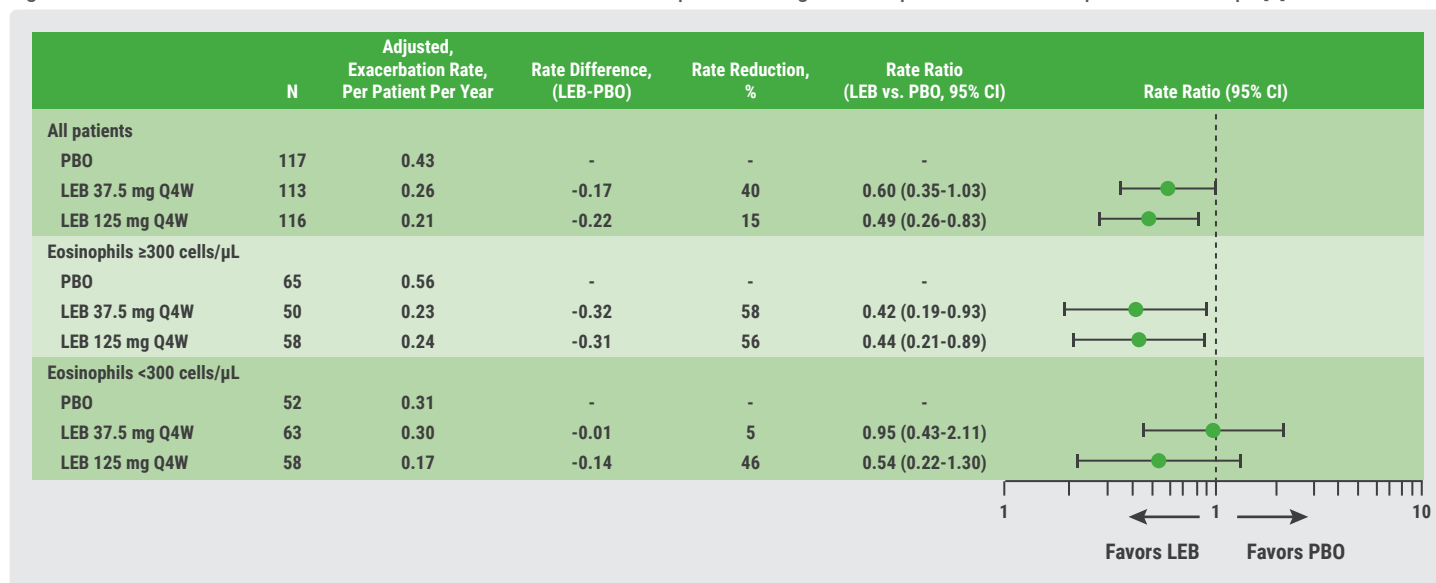
baseline blood eosinophil count of ≥ 300 cells/ μ L. In those with blood eosinophil counts of ≥ 300 cells/ μ L, the lebrikizumab 125 mg arm had a reduction of 56% (RR 0.44; 95% CI 0.21–0.89) in asthma exacerbation rates, but that rate was similar in the 37.5 mg arm with a 58% reduction (RR 0.42; 95% CI 0.19–0.93) (see Figure).

Most adverse events that occurred during the study were mild-to-moderate in severity and did not lead to discontinuation of the study drug. Eosinophil-associated, treatment-related adverse events included decreased neutrophil count and eosinophilia; there were no cases of eosinophilic granulomatosis with polyangiitis. “In terms of safety, it was pretty comparable to what was seen in the adult studies to date,” Prof. Szeffler said.

Prof. Szeffler concluded that there was a greater effect observed with the higher dose in the overall population and that exacerbation rates were trending toward further reduction in patients with baseline eosinophilia. He pointed out that, despite the lack of a consistent dose-response, post-hoc analyses of adult studies (e.g. LAVOLTA I and II, MILLY) showed similar results. This data collectively supports additional research into the optimal use of lebrikizumab with higher and more frequent dosing in patients with type 2 inflammation at risk for exacerbations.

1. Szeffler SJ, et al. Efficacy, Safety, and Tolerability of Lebrikizumab in Adolescent Patients with Uncontrolled Asthma (ACOUSTICS): A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study. Session B93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Figure: Reduction in asthma exacerbation rates with lebrikizumab versus placebo was greatest in patients with eosinophils ≥ 300 cells/ μ L [1]



CI, confidence interval; LEB, lebrikizumab; PBO, placebo; Q4W, every 4 weeks.

Type 2 asthma in children managed by dupilumab, despite atopic comorbidities

A post-hoc analysis of the phase 3 Liberty Asthma VOYAGE trial reported that dupilumab reduced severe asthma exacerbation rates and also improved overall lung function in children with moderate-to-severe asthma, independent of the presence of atopic comorbidities, including chronic rhinosinusitis, nasal polyps, or eosinophilic oesophagitis. A second presentation identified FeNO as a prognostic factor in the Liberty Asthma QUEST trial.

The Liberty Asthma VOYAGE trial ([NCT02948959](#)) evaluated the efficacy of dupilumab, a monoclonal antibody that blocks 2 primary drivers of type 2 inflammation (IL-4 and IL-13), every 2 weeks compared with placebo in children aged 6 to 11 years with uncontrolled, persistent asthma, and reported positive effects on severe asthma exacerbations in December 2021 [1]. A new post-hoc analysis of the Liberty Asthma VOYAGE trial took a look at the effect of dupilumab on comorbid atopic disorders and type 2 inflammation in that cohort [2].

For the current post-hoc analysis, presented by Prof. Theresa Guilbert (University of Cincinnati, OH, USA), 408 participants treated with dupilumab 100/200 mg or placebo were stratified by their burden of comorbid disease, into groups without any comorbid disease (dupilumab n=33; placebo n=28), with 1 comorbid phenotype (dupilumab n=91; placebo n=41), or with >1 ongoing comorbid disease (dupilumab n=149; placebo n=66). Participants were evaluated for a 52-week treatment period. Comorbid diseases were self-reported at baseline and included atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis (i.e. chronic rhinitis or chronic sinusitis), nasal polyposis, eosinophilic oesophagitis, food allergy, and hives. Participants were assessed via the annualised rate of severe asthma exacerbations and lung function, measured by change from baseline in percentage predicted prebronchodilator forced expiratory volume in 1 second (FEV₁pp).

The results indicated that severe asthma exacerbations were reduced among participants treated with dupilumab compared with those treated with placebo, irrespective of whether they presented with no comorbid disease (relative risk [RR] 0.284; 95% CI 0.072–1.117; Δ -71.6%; P=0.07), 1 ongoing comorbid disease (RR 0.980; 95% CI 0.438–2.194; Δ -2%; P=0.96), or >1 comorbid disease (RR 0.315; 95% CI 0.207–0.479; Δ -68.5%; P<0.0001). At 12 weeks, lung function improved most in patients with >1 atopic comorbidity treated with dupilumab;

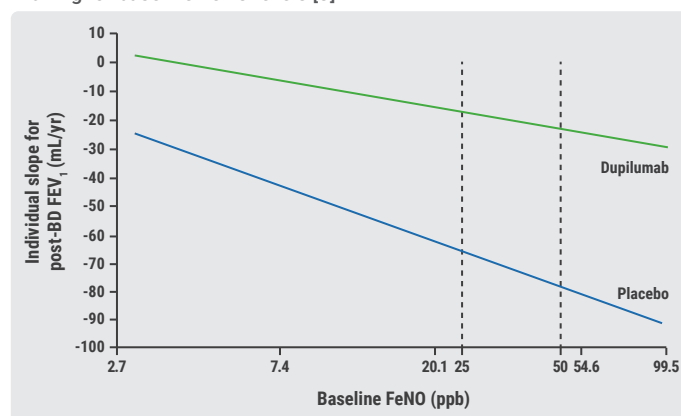
pre-bronchodilator FEV₁pp after 12 weeks was significantly improved by dupilumab treatment (1 comorbid disease: least square mean difference [LSMD] 5.37; 95% CI -0.18 to 10.93; P=0.058; >1 comorbid disease: LSMD 5.34; 95% CI 1.58–9.11; P=0.006), although no difference were observed in changes from baseline in pre-bronchodilator FEV₁pp among patients with no atopic comorbidities (LSMD -0.96; 95% CI -9.04 to 7.11; P=0.812). However, even for patients without any comorbid type 2 phenotype, after 52 weeks, dupilumab was associated with improvement in the change from baseline in pre-bronchodilator FEV₁pp for all patients compared with placebo: no comorbidities (LSMD 7.86; 95% CI 0.21–15.51; P=0.044), 1 comorbid disease (LSMD 5.87; 95% CI -0.64 to 12.38; P=0.077), and >1 comorbid disease (LSMD 7.26; 95% CI 3.17–11.36; P<0.001).

Prof. Guilbert concluded that dupilumab reduced severe exacerbation rates and by the end of treatment, had improved the percentage predicted pre-bronchodilator FEV₁ in children aged 6 to 11 years with uncontrolled, moderate-to-severe asthma, in patients with or without atopic comorbidities.

In a related talk, Prof. Ian Pavord (University of Oxford, UK) and colleagues used data from the Liberty Asthma QUEST study ([NCT02414854](#)) in order to identify biomarkers that may predict risk of lung function decline and response to dupilumab [3]. Multivariate regression analysis identified covariates that predicted lung function decline in placebo and dupilumab arms, with patients stratified by baseline exhaled nitric oxide (FeNO) levels and blood eosinophil levels.

Lung function decline at 52 weeks was similar between dupilumab and placebo across blood eosinophil levels; however, lung function decline difference increased in populations with higher baseline FeNO (see Figure).

Figure: Rate of lung function decline consistently increased in patients with higher baseline FeNO levels [3]



Because dupilumab attenuated lung function decline in patients with moderate-to-severe asthma, and patients with higher baseline FeNO levels demonstrated greater loss of lung function in placebo patients, Prof. Pavord pointed to a potential prognostic role of FeNO in identifying patients at risk of lung function decline. Furthermore, greater attenuation of loss of lung function after 1 year of dupilumab treatment indicated the potential predictive role of FeNO for dupilumab response. However, future, prospective studies are needed to validate FeNO as a biomarker.

1. Bacharier LB, et al. *N Engl J Med* 2021;385(24):2230–2240.
2. Guilbert TW, et al. Efficacy of dupilumab in pediatric patients with uncontrolled, moderate-to-severe asthma with and without ongoing atopic comorbid disease: LIBERTY ASTHMA VOYAGE Study. Session A2, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
3. Pavord I, et al. FeNO as a potential prognostic and predictive marker of lung function decline in patients with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA QUEST. Session B93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

NAVIGATOR steers asthma patients to tezepelumab

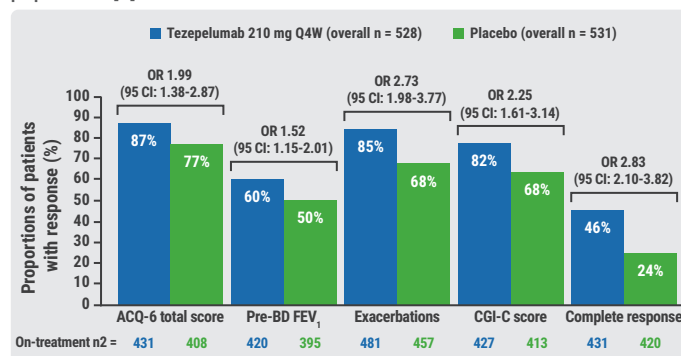
Patients with severe, uncontrolled asthma demonstrated overall 2.8-fold higher odds of improved clinical responses to tezepelumab than placebo, including exacerbation reduction, better asthma control, improved lung function, and clinician assessment.

Prof. Njira Lugogo (University of Michigan, MI, USA) presented a prespecified, on-treatment analysis of responses to tezepelumab using data from the completed phase 3, double-blind, placebo-controlled NAVIGATOR trial (NCT03347279) [1]. Participants aged 12–80 years were randomised to receive either subcutaneous injections of 210 mg tezepelumab (n=528) or subcutaneous placebo (n=531) every 4 weeks for 52 weeks while continuing to take their medium- or high-dose corticosteroid inhalers and at least 1 other asthma-control medication during the study.

The primary endpoint of annual asthma exacerbation rate at week 52 was met (see Figure). Across response criteria, the proportion of responders was higher in the tezepelumab than in the placebo group for exacerbation reduction (85.4% vs 67.5%; OR 2.73; 95% CI 2.04–3.90); Asthma Control Questionnaire (ACQ)-6 total score (86.9% vs 76.6%; OR 2.05; 95% CI 1.98–3.77); an improvement from baseline pre-bronchodilator forced expiratory volume in 1 second (FEV₁; 60.3% vs 49.9%; OR 1.52; 95% CI 1.15–2.01); and in Clinical Global Impression of Change (CGI-C) score (81.5% vs 67.7%; OR 2.25; 95% CI 1.61–3.14). The proportion of complete

responders (those who achieved significant improvement on all measures) was also greater in the tezepelumab group (46.2% vs 24.3%; OR 2.83; 95% CI 2.10–3.82).

Figure: Proportions of participants meeting clinical response criteria were higher with tezepelumab than placebo at week 52 in the on-treatment population [1]



ACQ, Asthma Control Questionnaire; CI, confidence interval; CGI-C, Clinical Global Impression of Change; pre-BD FEV₁, pre-bronchodilator forced expiratory volume in 1 second; OR, odds ratio; Q4W, every 4 weeks.

Prof. Lugogo concluded that “overall, these results add an important patient-level perspective to the primary study results.” Across each measure, tezepelumab recipients were more likely to have a response; the greatest difference observed was for exacerbation reduction. In addition, 48% of participants receiving tezepelumab had a complete response and achieved significant and clinically relevant improvements in all 4 response measures.

1. Lugogo N, et al. Clinical Responses to Treatment with Tezepelumab Among Patients with Severe, Uncontrolled Asthma in the Phase 3 NAVIGATOR Study. Session B93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

High-intensity interval training slashes daily corticosteroids in asthma

High-intensity interval training resulted in a 24% reduction in daily inhaled corticosteroids after 6 months without compromising asthma control, according to a new randomised controlled trial.

In a trial presented by Dr Anders Pitzner-Fabricius (Rigshospitalet Copenhagen, Denmark), physically inactive adults with persistent asthma were randomised 2:1 to either a regimen of high-intensity interval training 3 times per week for 6 months (n=102) or a control group of usual lifestyle (n=48) [1]. Both arms were followed up without intervention for an additional 6 months.

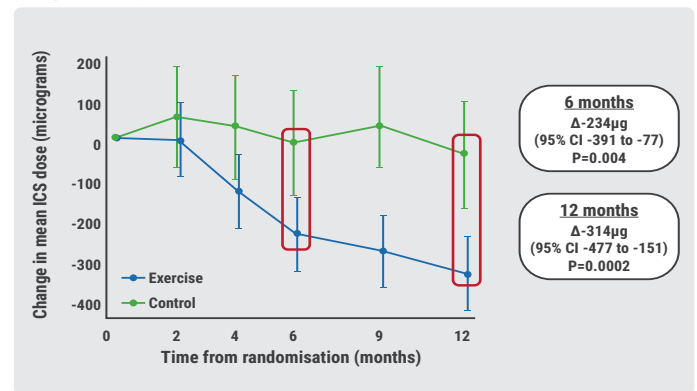
The results showed that the change in mean inhaled corticosteroid use (in micrograms) was reduced at 6 months in the high-intensity interval training arm by -234

micrograms (95% CI reduction -391 to -77; P=0.004), and even further by 12 months, even without intervention for the second 6-month period (-314 micrograms; 95% CI -477 to -151; P=0.002) (see Figure). When stratified by adherence to the high-intensity interval training regimen, the investigators reported that 71.4% of those with high adherence reduced their inhaled corticosteroid use by at least 25%, as opposed to 48.8% of the control group (P=0.09).

Dr Pitzner-Fabricius concluded that high-intensity interval training for adults with asthma has the potential to improve asthma control, reduce inhaled corticosteroid use, and has a potentially long-term positive lifestyle impact.

1. Pitzner-Fabricius A, et al. The effects of high-intensity interval training on inhaled corticosteroids dose in patients with asthma – a randomized controlled trial. Session A16, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Figure: High-intensity interval exercise resulted in a 24% reduction in daily inhaled corticosteroids versus control after 6 months, without compromising asthma control [1]



Chronic Obstructive Pulmonary Disease

Three's a crowd for triple therapy in COPD

A German registry study reported that patients with chronic obstructive pulmonary disease (COPD) who dropped the inhaled corticosteroid (ICS) component from their so-called triple-therapy regimen reported improved symptom control while experiencing fewer adverse effects.

Triple therapy is a common standard-of-care for COPD maintenance, consisting of a long-acting β -agonist (LABA), a long-acting muscarinic antagonist (LAMA), and an ICS. However, after achieving symptom control with triple therapy, it was unknown whether the ICS maintenance was really necessary or whether a LABA/LAMA combination is sufficient. This was the rationale for a real-world study, presented by Prof. Claus Vogelmeier (Philipps-University Marburg, Germany) [1].

The study included 340 patients who switched from triple therapy to a fixed-dose LABA/LAMA product and 784 who remained on triple therapy. The study was not randomised; as a result, some baseline differences between the groups were identified. Those remaining on triple therapy consisted of more men, participants had experienced longer average

duration of disease, and they had worse lung function than those who switched (58% of predicted forced expiratory volume in 1 second vs 67%). The study's primary endpoint was time to first COPD exacerbation.

The data showed that the 1-year risk was twice as high among participants remaining on triple therapy than those who had stepped down to dual therapy (HR 2.00; 95% CI 1.60–2.51). By month 12, nearly 60% of the triple-therapy group had experienced an exacerbation versus about 35% of those on dual therapy.

In addition, more participants in the step-down group obtained clinically relevant improvements in COPD Assessment Test (CAT) score. At baseline, those who remained on triplet therapy had an average CAT score of 20.0 compared with an average of 21.0 in the group who stepped down from their ICS therapy. At 1-year, improvement was seen in both groups, although the score dropped by 2 points (indicating a better outcome) for those who had stepped down to doublet therapy and by only 1 point for participants remaining on triple therapy. Of those who had stepped down, 58% had scores indicating clinically relevant improvement compared with 49% of those on triple therapy (P<0.001).

With regard to safety, dual therapy was safer during the 1-year follow-up. Not only was the total of all adverse events reduced, but also the number of those rated as serious. Even when exacerbations were discounted as adverse events, these results held steady.

1. Vogelmeier C, et al. Stepping Down from Triple Inhaled Therapy to a LABA/LAMA Fixed-Dose Combination: Data from the German Real-Life DACCORD COPD Cohort. Session C93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Higher 1-year COPD mortality after hospitalisation for White patients

A registry study using US Medicare and Medicaid records revealed that among patients hospitalised for chronic obstructive pulmonary disease (COPD), non-Hispanic White patients had the worst 1-year mortality rates.

Disparities in outcomes and processes of care are affected by race, geography (rural/urban), and socio-economic disadvantage (individual and neighbourhood). Dr Snigdha Jain (Yale School of Medicine, CT, USA) and colleagues sought to examine racial differences in long-term mortality after COPD hospitalisation in a universal, non-integrated healthcare system [1]. In addition, they wanted to determine whether differences could be attributable to geographic characteristics, receipt of post-acute care, or socio-economic characteristics.

Medicare records were screened for patients with a principal diagnosis of COPD or acute respiratory failure with a secondary diagnosis of COPD (n=244,624). The overall cohort was stratified into non-Hispanic White (n=209,208; 85.6%), non-Hispanic Black (n=19,887; 8.1%), Hispanic (n=10,264; 4.2%), or other (n=5,165; 2.1%). Unadjusted survival after 1 year of hospitalisation indicated that non-Hispanic Black patients had a 23% reduced risk of mortality compared with non-Hispanic White patients (HR 0.77; 95% CI 0.74–0.79). Adding geographic and socioeconomic characteristics did not mitigate this result (HR 0.78; 95% CI 0.76–0.80).

Dr Jain concluded that non-Hispanic White Medicare beneficiaries are at greater risk for mortality in the year following COPD hospitalisation compared with those of other race and ethnicity groups, even after accounting for rural or urban residence, as well as individual and neighbourhood socio-economic status.

1. Jain S, et al. Association Between Race, Geography, and 1-Year Mortality After Hospitalization for Chronic Obstructive Pulmonary Disease. Session A93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Reducing dyspnoea in chronic lung disease through weight loss

A small-scale study identified a positive impact on a remote weight-loss programme and reduced dyspnoea in patients with chronic lung disease.

Weight loss intervention to decrease breathlessness has previously shown promise in improving quality of life, reducing dyspnoea, and the number of exacerbations in patients with chronic lung disease [1]. This was the rationale for a small-scale study, presented by Dr Maria Benzo (Mayo Clinic Rochester, MN, USA) [2].

The study recruited 25 patients with a diagnosis of chronic lung disease who had a BMI >35 and dyspnoea of Medical Research Council class II or greater. Participants received 12 weeks of health coaching, Weight Watchers online programme with a daily food log, a fitness tracer wearable wristband, and a Bluetooth scale for weigh-ins at home.

The primary outcome measures were weight, quality of life, and dyspnoea improvement. Measurements were taken at baseline and at 3 and 6 months of follow-up. Of the 25 participants, only 13 finished the intervention, and data of only 10 was available at the 6-month follow-up. From baseline to 3 months, the average weight loss was 18.4 lbs (8.3 kg) or 6.9% of the total body weight (95% CI -25.2 to -11.7; P=0.00007). Likewise, dyspnoea was also reduced by 0.6 points (95% CI 0.2–1.1; P=0.00919). No other variables measured were significantly different, including quality of life, number of steps, or fatigue. At the 6-month follow-up, the average weight loss was 22.4 lbs (10.2 kg) or 9% of baseline body weight.

Dr Benzo concluded that acquiring healthy behaviours and self-awareness through registering food intake, checking daily steps, and weekly health coaching calls resulted in improved dyspnoea and weight loss.

1. Dupuy-McCauley KL, et al. *Chest*. 2020;158(3):1128–1131.
2. Benzo M, et al. Lifestyle Intervention Targeting Weight Loss to Reduce Dyspnea in Chronic Lung Disease. Session A93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

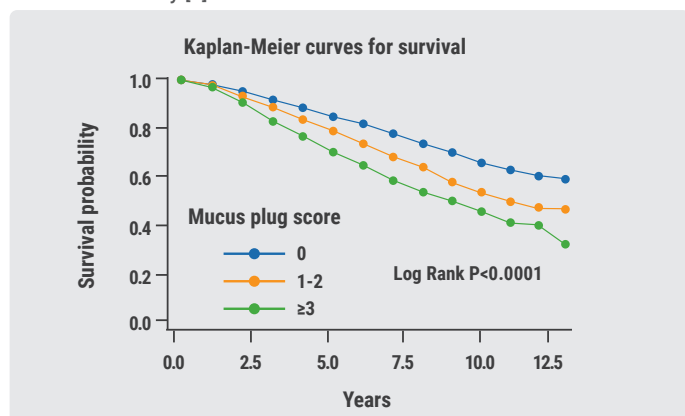
CT-evident mucus plugs in COPD associated with death

A case-control, observational, longitudinal study of patients with chronic obstructive pulmonary disease (COPD) determined that the detection of airway mucus plugs in CT scans is associated with all-cause mortality, as well as with respiratory and cancer deaths.

Mucus dysfunction is a central pathophysiologic feature of COPD that is measurable on CT and is associated with lung function impairment. The COPDGene Study ([NCT00608764](#)) aimed to assess whether airway mucus plugs detected on CT are associated with mortality in smokers with COPD [1]. The study observed 4,363 participants with COPD who were smokers and had CT images with mucus plugs scored. Prof. Alejandro Diaz (Brigham and Women's Hospital, MA, USA) presented the data.

With a median follow-up of 8.5 years, 1,490 patients had died (34%). A Kaplan-Meier analysis revealed that a high airway mucus plug score was associated with a higher risk of all-cause mortality (see Figure). Similarly, the mucus plug score was associated with a higher risk of respiratory and cancer deaths.

Figure: High airway mucus plug scores are associated with a higher risk of all-cause mortality [1]



Mucus plug score (No. of segments with mucus plugs)	Adjusted Model HR (95% CI)	Adjusted Model + Chronic bronchitis HR (95% CI)
0	Reference	Reference
1-2	1.14 (1.003-1.304)	1.14 (1.002-1.303)
≥3	1.24 (1.08-1.42)	1.22 (1.06-1.40)
		Chronic bronchitis HR 1.21 (1.08-1.37)

Prof. Diaz concluded that “the findings support airway mucus plugs as a clinically relevant imaging biomarker.”

1. Diaz A, et al. Airway Mucus Plugs and Mortality in COPD: Findings from the COPDGene Study. Session D14, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Home-based rehabilitation improves COPD: a randomised study

A multicentre, randomised, allocation-concealed, clinical trial generated for the first time prospective data

indicating improved clinical and psychosocial benefits of a 100% home-based rehabilitation programme for people with chronic obstructive pulmonary disease (COPD).

Dr Roberto Benzo (Mayo Clinic Rochester, MN, USA) explained that despite the fact that guideline-recommended pulmonary rehabilitation is the most effective, non-pharmacological therapy for people with COPD, programmes struggle with low participant uptake, poor adherence, and poor retention [1]. Although home programmes have been suggested previously as a potential means to address this unmet need, to date there have been no randomised studies in the USA to support the value of remote programmes.

The study design had 2 arms: the intervention arm (n=188) and the wait-list control group (n=187). All patients had baseline measures taken and the intervention group immediately began a 12-week remote monitoring plan described below. At 3 months, all measurements were retaken, at which point the wait-list control group began their 12-week intervention. Measurements were taken again at 6 months and at 9 months until the final analysis at 12 months.

The home-based rehabilitation system used a tablet that displayed a daily to-do list and provided videos to help guide exercise, but it was otherwise unsupervised. A pulse oximeter took home readings along with a regular questionnaire prompted by the programme to the health coach. The health coach then utilised the patient’s data to guide interactions in weekly calls.

The primary endpoint was the disease-specific physical and emotional quality of life after the 12-week intervention. Secondary endpoints included dyspnoea, mastery, emotions, fatigue, daily physical activity, sleep, depression, anxiety, and self-management.

The findings showed that 77% of participants completed the intervention. There was a significant difference in the intervention compared with the control group in the primary and secondary outcomes measured by Chronic Respiratory Disease Questionnaire (CRQ; see Table). Daily steps were increased by 655.83 in the intervention group (95% CI 148.03–1,163.64; $P < 0.0116$), self-management improved by 3.83 points (95% CI 1.85–5.79; $P < 0.001$), depression as measured by the PHQ-9 tool decreased in the intervention group by -1.2 points (95% CI -2.04 to -0.35; $P < 0.0056$), and total sleep time increased by 54 minutes (95% CI 6.74–102.96; $P < 0.025$).

Table: Results of the primary and secondary disease-specific quality of life outcome measures [1]

Measure	Intervention			Usual Care				P-value
	Mean (SD Score)			Mean (SD Score)				
	Baseline	12-week	Change in score, mean (95% CI)	Baseline	12-week	Change in score, mean (95% CI)	Adjusted difference, mean change (95% CI)	
Co-primary outcome								
CRQ* Physical summary score	3.8 (1.18)	4.36 (1.13)	0.56 (0.23, 0.51)	3.94 (1.13)	3.81 (1.20)	-0.13 (-0.29, -0.05)	0.54 (0.36, 0.73)	<0.001
CRQ* Emotional summary score	4.48 (1.18)	5.02 (1.02)	0.54 (0.28, 0.57)	4.50 (1.19)	4.48 (1.21)	-0.02 (-0.20, 0.05)	0.51 (0.31, 0.69)	<0.001
CRQ* Dyspnea	4.01 (1.42)	4.55 (1.40)	0.54 (0.21, 0.53)	4.21 (1.42)	4.01 (1.48)	-0.20 (-0.34, -0.05)	0.57 (0.35, 0.78)	<0.001
CRQ* Fatigue	3.57 (1.20)	4.14 (1.17)	0.57 (0.22, 0.55)	3.62 (1.18)	3.57 (1.20)	-0.05 (-0.27, 0.01)	0.52 (0.30, 0.74)	<0.001
CRQ* Emotions	4.55 (1.17)	5.05 (1.00)	0.50 (0.24, 0.54)	4.57 (1.19)	4.55 (1.21)	-0.02 (-0.21, 0.05)	0.47 (0.27, 0.66)	<0.001
CRQ* Mastery	4.35 (1.41)	4.97 (1.30)	0.62 (0.32, 0.67)	4.38 (1.40)	4.35 (1.41)	-0.03 (-0.25, 0.11)	0.56 (0.32, 0.81)	<0.001

Dr Benzo concluded that this home-based intervention represents an opportunity to increase the uptake of rehabilitation in COPD, across geographies and socioeconomic classes, and to provide options of remote care that are now in

increased demand in the context of the COVID-19 pandemic.

1. Benzo R, et al. Effect of Home-Based Rehabilitation with Health Coaching on Chronic Obstructive Pulmonary Disease Outcomes: A Randomized Study. Session A16, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Highlighted Advances

Novel P2X3 antagonist can SOOTHE chronic cough

New phase 2b data of the SOOTHE trial showed a clinical benefit for the investigational P2X3 antagonist BLU-5937 for chronic cough, with fewer side effects than in previous trials.

Prof. Jaclyn Smith (University of Manchester, UK) presented the findings of the SOOTHE study [1]. The rationale behind the study is that refractory chronic cough typically lasts >8 weeks and does not respond to treatment of possible associated disease or is simply not associated with a disease. There are no approved treatment options. Hypersensitisation of cough signalling pathways, including the P2X3 receptor, is thought to play a key role in refractory chronic cough, and P2X3 antagonists have shown some promise in clinical trials [2].

SOOTHE is a randomised, double-blind, placebo-controlled, parallel-arm, dose-finding, phase 2b trial ([NCT04678206](#)) of the investigational drug BLU-5937, which is a P2X3 antagonist with high selectivity. After a 3-week run-in period,

249 enrolled participants with more than 25 awake coughs/hour were randomised to either placebo twice daily (n=63) or to BLU-5937 12.5 mg (n=62), 50 mg (n=62), or 200 mg twice daily (n=62). In addition, 61 participants whose baseline cough frequency was between 10–25 coughs/hour were randomised to receive either placebo (n=30) or BLU-5937 200 mg twice daily (n=31). Treatment was provided for 28 days, and follow-up continued until day 43, 2 weeks after the final dose. Demographics and baseline characteristics were well-balanced across all treatment arms. The primary endpoint of the trial was change in objective cough frequency, as measured over 24 hours and calculated in the log-transformed geometric means ratio.

The results showed that the higher doses of BLU-5937 of 50 mg and 200 mg met the primary endpoint. The placebo-adjusted change in 24-hour cough frequency in the 12.5 mg arm dropped by 18.3% at day 15, and by 21.1% at day 28; although those reductions were not significant. However, for the 50 mg and 200 mg arms, coughing was reduced by 32–34% at day 15, which was sustained at 34% at day 28,

with all measurements being significant (2-sided $P < 0.005$). The absolute change in cough frequency was 53% for both 50 mg and 200 mg doses from baseline compared with a 28% absolute reduction in the placebo arm. The dose-finding part of the trial concluded that there was a dose-response between 12.5 and 50 mg, with no additional clinical benefit observed beyond 50 mg.

With regard to safety, no serious adverse events were reported, and similar mild adverse events were reported for placebo as for BLU-5937. Notably, mild taste disturbances were reported in the BLU-5937 arms, although none resulted in partial or total loss of taste. Prof. Smith concluded that both the important reductions in cough frequency as well as the observed, favourable safety profile support the continued clinical development of this P2X3 antagonist.

1. Smith JA, et al. Safety and efficacy of BLU-5937 in the treatment of refractory chronic cough from the phase 2b SOOTHE trial. Session C93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Abdulqawi R, et al. Lancet. 2015;385\(9974\):1198–205.](#)

Colistimethate sodium PROMISing for non-cystic fibrosis bronchiectasis

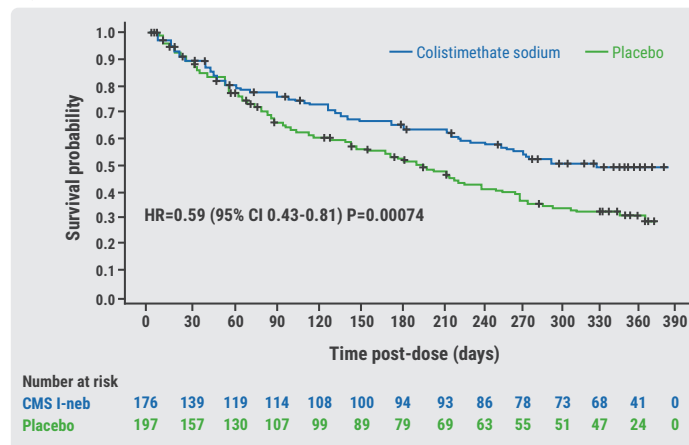
In the phase 3 PROMIS clinical programme, the use of colistimethate sodium powder for nebulisation solution reduced pulmonary exacerbations in adults with non-cystic fibrosis bronchiectasis (NCFB) and *Pseudomonas aeruginosa*.

The phase 3 PROMIS clinical programme ([NCT03093974](#)), consisting of the PROMIS-I (n=377) and PROMIS-II (n=287) trials, was designed to evaluate the safety and efficacy of colistimethate sodium powder for nebulisation solution in patients with NCFB who are chronically infected with *P. aeruginosa* [1]. Dr Charles Haworth (Royal Papworth Hospital, UK) presented the results.

After 12 months, twice-daily administration of nebulised colistimethate sodium powder (n=177) significantly reduced annual pulmonary exacerbation rates compared with placebo (n=200; 0.58 vs 0.95 per patient per year; rate ratio [RR] 0.61; 95% CI 0.46–0.82; $P = 0.001$); thus, meeting the primary endpoint of the trial. The treatment effect was larger in adherent participants (43.5% reduction in exacerbations; $P < 0.001$). The trial also met important secondary endpoints, demonstrating improvements compared with placebo regarding prolonged time to first exacerbation in the nebulised colistimethate sodium powder group (HR 0.59; 95% CI 0.43–0.81; $P < 0.001$, see Figure). The frequency of severe exacerbations was also reduced (RR 0.41;

95% CI 0.23–0.74; $P = 0.003$). Quality of life, measured by the St. George's Respiratory Questionnaire (SGRQ), significantly improved with colistimethate sodium powder, with a 4.55 point difference versus placebo after 12 months of treatment ($P = 0.006$). After 28 days of treatment, *P. aeruginosa* density was significantly reduced in the treatment arm ($P < 0.001$). The percentage of patients with adverse events was similar between groups. Bronchospasm and antibiotic resistance were infrequently observed (2.8% and 1%, respectively).

Figure: Time to first exacerbation in PROMIS [1]



“The PROMIS data shows that colistimethate sodium powder taken twice daily through nebulisation solution reduces exacerbation frequency and improves quality of life in people with bronchiectasis and chronic *P. aeruginosa* infection,” summarised Dr Haworth. “The data also demonstrates that 12 months of treatment is well tolerated. These results are encouraging for patients as there is currently no approved drug treatment for this indication.”

1. Haworth C, et al. Efficacy and Safety of Colistimethate Sodium Delivered Via the I-Neb in Patients with Bronchiectasis and *Pseudomonas Aeruginos*. Session B12, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

Is avacopan better than prednisone for respiratory ANCA-associated vasculitis outcomes?

An exploratory subgroup analysis of the phase 3 ADVOCATE trial showed that avacopan was only somewhat better than prednisone at reducing respiratory, as well as ear, nose, and throat (ENT), involvement in patients with ANCA-associated vasculitis. However, reduced glucocorticoid use in the avacopan group was a clear clinical benefit.

Prof. Ulrich Specks (Mayo Clinic, MN, USA) presented the respiratory and ENT outcomes of the phase 3 ADVOCATE trial

([NCT02994927](#)) [1]. ADVOCATE was a phase 3, randomised, double-blind, double-dummy, controlled clinical study comparing the selective neutrophil C5aR inhibitor avacopan (plus prednisone-matching placebo) with prednisone (plus avacopan-matching placebo) in addition to either cyclophosphamide (followed by azathioprine) or rituximab. The previously published primary results demonstrated the efficacy of avacopan in helping patients with ANCA-associated vasculitis achieve disease remission at 6 months and sustained remission at 12 months [2].

When the 330 patients included in the current subgroup analysis were stratified by the phenotype of their disease, pulmonary involvement was more common in patients with granulomatosis with polyangiitis (54%; 98/181) than with microscopic polyangiitis (30%; 45/149). The primary endpoint was the percentage of participants achieving disease remission at week 26 and sustained remission at week 52. Disease remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and no glucocorticoids within 4 weeks prior to week 26. Sustained remission was remission at week 26 and week 52 and no glucocorticoid use at 4 weeks prior to week 52. Lung and ENT involvement was defined as BVAS-detected active vasculitis in the upper and lower respiratory tract.

The results indicated an overall glucocorticoid use reduction by a median of 86% in the avacopan group, with data pointing to a 26-week non-inferiority significance, improving to a 52-week superiority significant remission compared with the prednisone group. Although rates of both lung and ENT involvement were numerically lower in the avacopan group than in the prednisone group, the differences were not statistically significant. At baseline, 43% of patients (143/330) had evident lung involvement. At weeks 26 and 52, lung involvement was present in 0.6% (1/166) and 0% (0/166) of participants in the avacopan group, respectively. In comparison, at weeks 26 and 52, 2.4% (4/164) and 1.8% (3/164) of participants in the prednisone group, respectively, had lung involvement. Similarly, ENT involvement at baseline was present in 44% of participants (144/330). In the avacopan group, ENT involvement was present in 1.2% (2/166) of participants at both weeks 26 and 52. In the prednisone group, ENT involvement was present in 3.7% (6/164) and 3.0% (5/164) of participants, at weeks 26 and 52, respectively.

“The overall results of the ADVOCATE trial are very exciting as they indicate that patients with ANCA-associated vasculitis

receiving avacopan can achieve sustained remission with minimal glucocorticoid exposure,” Prof. Specks said. “While the results presented here for the subset of patients with lung and ENT involvement are most promising, the specific effect of avacopan on individual disease manifestations requires further study.”

1. Specks U, et al. Insights from the ADVOCATE study: Respiratory tract involvement in patients with ANCA-associated vasculitis in a randomised, double-blind, placebo-controlled phase 3 trial of avacopan. Session C93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Jayne DRW, et al. N Engl J Med 2021;384\(7\):599–609.](#)

PAGANINI phase 2b data promising for eliapixant

The 12-week dose-ranging results of the phase 2b PAGANINI trial indicated efficacy of the selective P2X3 antagonist eliapixant in patients with refractory chronic cough, although a single liver safety signal warrants intensified monitoring going forward.

Prof. Peter Dicipinigaitis (Albert Einstein College of Medicine, NY, USA) presented the efficacy and safety data of eliapixant on chronic cough [1]. He explained that P2X3 receptors regulate afferent sensory nerve fibre ATP-mediated signalling, which in turn is thought to play an important role in sensory neural dysregulation associated with chronic cough. Eliapixant is a selective P2X3 receptor antagonist with greater potency and selectivity for the human P2X3 homotrimer than the P2X2/3 heterotrimer receptor [2].

To test the effect of eliapixant on chronic cough, the randomised, phase 2b PAGANINI ([NCT04562155](#)) enrolled 310 patients with refractory chronic cough lasting ≥ 12 months. Participants were randomised to 12 weeks of treatment with twice-daily placebo (n=77), or eliapixant 25 mg (n=75), 75 mg (n=78), or 150 mg (n=80). Baseline characteristics were reasonably well-balanced among the groups. The primary endpoint was the change from baseline in 24-hour cough frequency.

The results showed that a significant dose-response signal was established, with one-sided P-values of ≤ 0.1 . From baseline to week 12, 24-hour cough count decreased with eliapixant for twice-daily doses of 25 mg, 75 mg, or 150 mg, respectively: -44%, -54%, -49%, compared with -34% for placebo. Awake cough count also decreased: -44%, -54%, and -53%, respectively, compared with -33% for placebo.

Mild adverse events were reported for both the placebo as well as eliapixant arms, and 1 serious hepatic adverse event

of drug-induced liver injury did occur in a single individual in the 150 mg eliapixant arm, which spontaneously resolved upon discontinuation. Some taste- and smell-related adverse events were reported in 24% of participants in the eliapixant highest dose arm, although that decreased to background at 25 mg.

Prof. Dicipinigaitis concluded that eliapixant: (1) reduced 24-hour cough count versus placebo, with a safety and tolerability profile similar to other studies of eliapixant; (2) warrants intensified liver monitoring due to the single case of drug-induced liver injury; and (3) was associated with fewer taste-related adverse events in PAGANINI than reported in other trials with non-selective P2X3 antagonists.

1. Dicipinigaitis P et al. Eliapixant in refractory chronic cough: the 12-week randomized, double-blind, placebo-controlled phase 2 PAGANINI trial. Session C93, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Davenport AJ, et al. *Sci Rep.* 2021;11\(1\):19877.](https://doi.org/10.1038/s41598-021-19877-7)

New guidelines for IPF and PPF

A team of multidisciplinary experts reviewed and updated the clinical practice guidelines for idiopathic pulmonary fibrosis (IPF) and presented them at ATS 2022. They also defined progressive pulmonary fibrosis (PPF) in patients with non-IPF interstitial lung diseases (ILDs) and made recommendations with regard to the treatment of this condition. These recommendations were recently published.

Dr Elizabeth Renzoni (Royal Brompton Hospital, UK), who presented the new guidelines at ATS 2022, explained that IPF can be identified through radiological and histologic characteristics of usual interstitial pneumonia (UIP) [1,2]. A diagnosis of UIP via biopsy is based on a set of histopathological features. Although transbronchial lung cryobiopsy (TBLC) is more likely to detect a probable UIP pattern than a definite UIP pattern compared with surgical lung biopsy (SLB), a novel systematic review has been published since the development of the IPF guidelines of 2018, demonstrating that TBLC may be a valid alternative to SLB in experienced centres [3,4]. Therefore, the committee made the conditional recommendation that TBLC may be an alternative to SLB when making a histopathological diagnosis in patients with ILD.

The committee did not make a recommendation for the use of an additional genomic classifier test in patients with ILD who are being diagnosed for UIP through transbronchial forceps biopsy, due to a lack of consensus between the members. Although the systematic review that was analysed

to make an informed decision on this topic did not lead to a recommendation, the experts agreed that the use of genomic classifier testing should be revised if new studies are being published [5].

Furthermore, 2 treatment-related recommendations were made. Firstly, a conditional recommendation was made to not use antacid medication in patients with IPF if the goal is to improve respiratory outcomes. A recently published systematic review did not reveal definitive benefits of antacid medication to treat respiratory issues in patients with IPF [6]. However, antacid medication may still be appropriate in patients with IPF and gastro-oesophageal reflux disease (GERD) for treating GERD-related outcomes.

Additionally, the committee made the conditional recommendation that patients with IPF should not be referred to anti-reflux surgery with the goal of improving respiratory outcomes. The systematic review analysing this matter did not demonstrate a significant respiratory benefit for this type of surgery in patients with IPF but did show that surgical complications occurred in approximately 15% of the patients [6]. Nonetheless, anti-reflux surgery may still be appropriate in patients with IPF to treat GERD-related outcomes.

A definition of PPF in patients with non-IPF ILD

In patients with ILD, other than IPF, and with radiological evidence of pulmonary fibrosis, PPF was defined by the committee as the occurrence of at least 2 of the following 3 features, within the last 12 months, if no alternative explanation was present: worsening of respiratory symptoms, physiological evidence of disease progression, and radiological evidence of disease progression.

In addition, the committee made a conditional recommendation to use nintedanib for the treatment of PPF in patients with fibrotic ILD (other than IPF) who failed on standard management but emphasised that research is needed to establish the performance of nintedanib in specific ILDs that display PPF. This recommendation was based on a systematic review that demonstrated significant efficacy of nintedanib in patients with PPF, measured as the annual decline of forced vital capacity (FVC), without persistent adverse events if the therapy was discontinued [7].

Finally, the experts recommended that research needs to be conducted to assess the efficacy, effectiveness, and safety of pirfenidone in patients with non-IPF ILD who display

PPF. Although the committee agreed that pirfenidone is a promising therapy for PPF, the systematic review that was studied by the group did not provide sufficient evidence to make a recommendation.

1. Renzoni E, et al. Recent ILD Guidelines. Session PG10, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Raghu G, et al. Am J Respir Crit Care Med. 2022;205\(9\):e18–e47.](#)
3. [Kheir F, et al. Ann Am Thorac Soc. 2022. Doi:10.1513/AnnalsATS.202102-1980C.](#)
4. [Raghu G, et al. Am J Respir Crit Care Med 2018;198:e44–e68.](#)
5. [Kheir F, et al. Ann Am Thorac Soc. 2022;19\(5\):827–832.](#)
6. [Khor YH, et al. Ann Am Thorac Soc. 2022;19\(5\):833–844.](#)
7. [Ghazipura MHM, et al. Ann Am Thorac Soc. 2022; May 2. Doi:10.1513/AnnalsATS.202103-343OC.](#)

POISE-3: Tranexamic acid for non-cardiac surgery

The POISE-3 clinical trial compared the use of antifibrinolytic tranexamic acid with placebo in patients undergoing non-cardiac surgery who are at risk of a peri-operative cardiovascular event. The efficacy endpoint favours a wider use of tranexamic acid at the start and end of non-cardiac surgery. Although a small difference in composite cardiovascular complications between the tranexamic acid group and the placebo group was observed, the non-inferiority of tranexamic acid was not established, making it a new option for patients.

Prof. Philip Devereaux (McMaster University, Canada) presented the international, multicentre, randomised POISE-3 study ([NCT03505723](#)) during the late-breaking session for high-impact publications in critical care, as the results were just recently published in the *New England Journal of Medicine* [1,2]. POISE-3 randomised 9,535 patients undergoing non-cardiac surgery 1:1 to receive either 1 g intravenous bolus of tranexamic acid or placebo at the start and end of surgery [1]. The primary efficacy endpoint for the evaluation of tranexamic acid was a composite bleeding outcome comprising life-threatening bleeding, major bleeding, or bleeding into a critical organ at 30 days. The primary cardiovascular safety endpoint was a composite cardiovascular outcome, comprising myocardial injury after non-cardiac surgery, non-haemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism at 30 days.

After 1 month, a composite bleeding event occurred in 9.1% in the tranexamic acid group and 11.7% in the placebo group (HR 0.76; 95% CI 0.67–0.87; $P < 0.001$). Additionally, there was no difference in the safety composite cardiovascular endpoint: events occurred in 14.2% of the tranexamic acid arm and 13.9% of the placebo group (HR 1.02; 95% CI 0.92–1.14; $P_{\text{non-inferiority}} = 0.04$).

Prof. Devereaux concluded that among patients undergoing non-cardiac surgery, the incidence of the composite bleeding outcome was significantly lower with tranexamic acid than with placebo, with no significant safety burden associated with this treatment.

1. Devereaux PJ, et al. Efficacy And Safety Of Tranexamic Acid In Patients Undergoing Noncardiac Surgery: The Poise-3 Trial. Session A84, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Devereaux PJ, et al. N Engl J Med 2022; Apr 02. DOI: 10.1056/NEJMoa2201171.](#)

Obstructive sleep apnoea in most children with pulmonary hypertension

New data from paediatric patients with pulmonary hypertension (PH) found that a majority are affected by obstructive sleep apnoea (OSA), prompting investigators to suggest routine screening for OSA in this population.

Dr Daniel Ignatiuk (Cincinnati Children's Hospital, OH, USA) presented a retrospective study analysing OSA risk factors documented in a 10-year cohort of paediatric patients with PH at the Cincinnati Children's Hospital, between January 2010 and August 2020 [1]. Identified were 403 patients aged 0-21 years who underwent diagnostic polysomnogram (PSG), including 89 patients with a documented diagnosis of PH (median age 3.6 years; range 9 days to 17.6 years). These 89 patients were sub-classified based on their PH group: group 1 (n=25; 28.1%), group 3 (n=31; 34.8%), and group 1/3 for patients meeting both group 1 and 3 criteria (n=33; 37.1%). Group 2 consisted of only 2 patients and was excluded from the analysis due to the low number.

Diagnosed sleep disorders included OSA (n=79; 88.8%), central sleep apnoea (n=11; 12.4%), hypoventilation (n=6; 6.7%), non-apnoeic hypoxaemia (n=28; 31.5%), and periodic limb movement disorder (n=5, 5.6%). OSA risk was increased with a diagnosis of trisomy 21 (RR 1.24; 95% CI 1.09–1.42; $P < 0.05$).

However, OSA risk was decreased in group 1 compared with group 1/3 PH (RR 0.84; 95% CI 0.71–0.99; $P < 0.05$) or group 3 PH (RR 0.81; 95% CI 0.68–0.96; $P < 0.05$), and no difference in OSA risk between group 1 and group 3 PH was observed.

The take-home message for this study was that OSA was diagnosed in a majority of paediatric patients, most notably in patients with trisomy 21 or PH classification meeting both group 1 and 3 criteria. "Our research supports routine screening for OSA in this population, especially," concluded Dr Ignatiuk.

1. Ignatiuk D, et al. Risk for Obstructive Sleep Apnea in Pediatric Patients with Pulmonary Hypertension. Session A68, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

No screening evidence for COPD

Asymptomatic adults should not be screened for chronic obstructive pulmonary disease (COPD), the US Preventive Services Task Force (USPSTF) stated with moderate certainty based on evidence that there was no net benefit.

Because COPD is the 6th leading cause of death in the USA, the USPSTF re-reviewed screening evidence of asymptomatic individuals, after their D-level recommendation against screening in asymptomatic adults was originally issued in 2016. Their results and recommendations were presented by Prof. Carol Mangione (University of California at Los Angeles, CA, USA), and published in *JAMA* [1,2]. After a review of all new evidence, the USPSTF re-affirmed its previous recommendation that COPD civilian screening has no net benefit for asymptomatic adults.

The Task Force stressed that their recommendation only applies to adults with no respiratory symptoms; anyone with symptoms such as a chronic cough, sputum, breathing difficulties, or wheezing, should consult a specialist and take action. The USPSTF also pointed out that factors such as cigarette smoking could increase a person's risk for COPD. Cigarette smoking is the leading cause of COPD in the USA, with approximately 15% of current smokers and 8% of former smokers reporting a diagnosis of COPD.

The Task Force reviewed new data from 6 treatment trials and 2 observational trials that focused on pharmacologic or non-pharmacologic treatment harms in adults with mild-to-moderate or minimally symptomatic COPD. Prof. Mangione noted that among the trials that reported adverse events, no significant harms were recorded.

Prof. Mangione noted that it is still unclear whether early treatment for asymptomatic, minimally symptomatic, or screen-detected populations would slow disease progression. "The USPSTF found no new substantial evidence that could change its recommendation and, therefore, re-affirms its recommendation against screening for COPD in asymptomatic adults."

1. Mangione C, et al. Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Reaffirmation Recommendation Statement. Session A84, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [US Preventive Services Task Force. JAMA. 2022;327\(18\):1806-1811.](https://doi.org/10.1001/jama.2022.3271806-1811)

Novel PDE4B inhibitor offers breakthrough for IPF

Findings from a phase 2, randomised, placebo-controlled trial in patients with idiopathic pulmonary fibrosis (IPF)

showed that the investigational drug BI 1015550, either alone or with background use of an antifibrotic agent, significantly prevented a decrease in lung function.

The anti-inflammatory and immunomodulatory abilities of oral, selective phosphodiesterase 4B (PDE4B) inhibition had not yet been explored clinically for IPF. Prof. Luca Richeldi (Università Cattolica del Sacro Cuore, Italy) presented the first clinical results of the novel, investigational, preferential, oral PDE4B inhibitor BI 1015550 with or without background antifibrotics in a phase 2 study ([NCT04419506](https://doi.org/10.1186/1745-7581-19-506)) [1]. The findings were simultaneously published in the *New England Journal of Medicine* [2].

IPF is a progressive, irreversible lung disease with high mortality. Currently, 2 antifibrotic drugs (i.e. nintedanib and pirfenidone) have been approved that slow but do not stop fibrotic progression [3,4]. There remains an unmet need for additional treatments that can be used alone or with existing antifibrotic therapies. In preclinical studies, the preferential PDE4B inhibitor BI 1015550 demonstrated anti-inflammatory and antifibrotic effects [5].

The participants were randomised to receive either 18 mg of the investigational drug oral twice daily (n=97) or placebo (n=50) for 12 weeks, with an additional 1 week of follow-up. Randomisation was based on stratification of use of antifibrotics. The primary endpoint was change in baseline in forced vital capacity (FVC) at 12 weeks. The secondary endpoint was the percentage of participants with treatment-emergent adverse events.

The primary endpoint was evaluated separately in participants with and without background antifibrotic therapy at baseline in a 2-step procedure. Firstly, data from the current trial were analysed with a restricted maximum likelihood-based approach using a mixed model with repeated measurements (MMRM). Secondly, the pre-specified primary analysis of FVC change was based on a Bayesian approach combining MMRM estimates and historical data for the placebo arm.

The primary endpoint was met; the change in FVC at week 12 and over time in all participants showed a remarkable improvement in the participants taking the investigational drug with an adjusted mean of +4.6 mL versus -83.8 mL for the placebo arm (Δ 88.4 mL; 95% CI 40.7–136.0). When stratifying the groups based on background antifibrotic therapy, the effect was maintained; using Bayesian modelling, patients

without background antifibrotics showed a +5.7 mL mean improvement in FVC vs -81.4 mL (Δ 87.1 mL) and those with background antifibrotics had a +2.9 mL FVC improvement on the drug as opposed to a -59.2 mL decrease in the placebo (Δ 62.1 mL). Both calculations predicted a >98% probability that BI 1015550 is superior to placebo. The trial also met the secondary endpoint, as BI 1015550 demonstrated acceptable safety and tolerability in trial participants over 12 weeks.

In conclusion, compared with placebo, treatment with the investigational PDE4B inhibitor BI 1015550, either alone or concomitant with background antifibrotic agents, prevented a decline in lung function in patients with IPF. The observed safety and tolerability of BI 1015550 were acceptable and, in combination with the beneficial effects on FVC, warrant further clinical development as a treatment for IPF and possibly other forms of progressive pulmonary fibrosis.

1. Richeldi L, et al. Phosphodiesterase Inhibition as a Novel Strategy to Stop Fibrosis in the Lung. Session B12, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Richeldi L, et al. N Engl J Med 2022. Doi: 10.1056/NEJMoa2201737.](#)
3. [Richeldi L, et al. N Engl J Med 2014;370\(22\):2071–2082.](#)
4. [Noble PW, et al. Eur Respir J. 2016;47\(1\):243–253.](#)
5. [Herrmann FE, et al. Front Pharmacol. 2022;13:838449.](#)

Hydrocortisone does not help preterm infants

Hydrocortisone treatment in preterm infants, starting on postnatal day 14 to 28, did not result in substantially higher survival without moderate or severe bronchopulmonary dysplasia (BPD) than placebo, according to the results of a randomised trial.

Prof. Namasivayam Ambalavanan (University of Alabama, AL, USA) introduced the rationale for the study by stating that BPD is a prevalent complication after an extremely preterm birth (<30 weeks gestation), which may partially be attributable to inflammation as a result of mechanical ventilation. It is unknown whether hydrocortisone treatment after the first postnatal week might be able to improve survival without BPD [1]. To that end, researchers determined the efficacy of hydrocortisone in facilitating extubation, thereby increasing survival without moderate or severe BPD, by initiating the Hydrocortisone and Extubation study ([NCT01353313](#)). The study was also recently published in the *New England Journal of Medicine* [2].

Infants (n=800) with a gestational age <30 weeks (mean birth weight 715±167 g; mean gestational age 24.9±1.5 weeks) who had been intubated for at least 7 days at 14 to 28 days of life were randomised to receive either hydrocortisone (4 mg/kg

body weight/day tapered over 10 days) or placebo. The primary efficacy endpoint was the use of respiratory support at 36 weeks postmenstrual age or survival without moderate or severe BPD. The primary safety endpoint was survival without moderate or severe neurodevelopmental impairment at 22–26 months adjusted age.

At 36 weeks, survival without BPD was reported in 66 of 398 infants (16.6%) in the hydrocortisone arm and in 53 of 402 (13.2%) in the placebo arm (adjusted rate ratio 1.27; 95% CI 0.93–1.74; not significant). For the safety endpoint, there was also no difference observed at 2 years follow-up; survival without moderate or severe neurodevelopmental impairment occurred in 36.9% in the hydrocortisone arm and in 37.3% in the placebo arm (adjusted rate ratio 0.98; 95% CI 0.81–1.18; not significant). Furthermore, although most adverse events occurred at similar rates in both groups, hypertension requiring treatment was more common in the hydrocortisone arm than in the placebo arm (4.3% vs 1.0%).

Enrolled children are being seen at 5–6 years for further follow-up.

1. Ambalavanan N, et al. The effect of hydrocortisone on survival without BPD at 36 weeks and on neurodevelopmental impairment (NDI) at 2 years in intubated infants born <30 weeks GA. Session A2, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Watterberg KL, et al. N Engl J Med 2022;386\(12\):1121–1131.](#)

CPAP temporarily supports pulmonary oxygenation in morbidly obese patients

In a prospective, randomised-controlled trial, morbidly obese patients with normal lung function using post-extubation continuous positive airway pressure (CPAP) showed improved pulmonary oxygenation; however, oxygenation did not persist after termination of CPAP.

The rationale behind the study, Dr Felix Gırrbach (University Hospital of Leipzig, Germany) explained, was that mechanical ventilation with individualised positive end-expiratory pressure (PEEP_{IND}) in combination with continuous CPAP support in the initial hours following extubation is associated with better oxygenation compared with the use of PEEP alone [1].

In this study, 46 participants with a BMI of >35 kg/m² who were scheduled to undergo bariatric laparoscopic abdominal surgery were ventilated with PEEP_{IND}, which was defined as “the PEEP value with the lowest regional ventilation inhomogeneity as determined by electrical impedance tomography (EIT) during a standardised decremental PEEP-trial.”

The participants were randomised to a group that received CPAP (n=21) or a control group (n=25). Baseline characteristics were similar in both groups, with a mean age of 44 years of age and a mean BMI of 46.9 kg/m². The participants in the CPAP arm received continuous CPAP support for 2 hours after extubation compared with standard supportive care for individuals in the control arm, including supplemental nasal oxygen insufflation to oxygen saturation (SpO₂) level of ≥90%. Arterial oxygen partial pressure (PaO₂)/fractional inspired oxygen (FiO₂) ratio was measured 2 hours and 4 hours after extubation, respectively.

Dr Girrbach reported that there was no difference between the groups with regard to the median PEEP_{IND}, which was roughly 18 cmH₂O in both arms (P=0.76). However, although oxygenation (PaO₂/FiO₂ ratio) prior to extubation was comparable between the 2 arms (P=0.32), the PaO₂/FiO₂ ratio in the CPAP group was significantly higher during CPAP support (472 mmHg in the intervention arm vs 317 mmHg in the control arm; P<0.001).

Dr Girrbach suggested that despite post-extubation CPAP support in morbidly obese patients with normal lung function, the improvement in oxygenation did not persist after termination of CPAP support, potentially pointing to atelectasis formation.

1. Girrbach F, et al. Post-extubation CPAP support and oxygenation in morbidly obese patients – a prospective randomized controlled trial. Session A63, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.

ISAACC trial: CPAP controls blood pressure in ACS patients with severe OSA

A post-hoc analysis of the multicentre, randomised controlled ISAACC trial demonstrated that, in patients with acute coronary syndrome (ACS) with severe obstructive sleep apnoea (OSA), secondary hypertension can be well managed by continuous positive airway pressure (CPAP).

The main objective of the multicentre, open-label, parallel group, randomised controlled ISAACC trial ([NCT01335087](https://clinicaltrials.gov/ct2/show/study/NCT01335087)) was to determine whether CPAP treatment is able to reduce the incidence of cardiovascular events (i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, and hospitalisation for

unstable angina or transient ischaemic attack) in patients with ACS and OSA. The primary purpose of the current post-hoc analysis, presented by Dr Manuel Sánchez De La Torre (Lleida Biomedical Research Institute, Spain), was to determine the long-term effects on blood pressure; the results were recently published [1,2].

The analysis included 1,803 patients who were admitted to hospital for ACS symptoms and underwent respiratory polygraphy during the first 24–72 hours after admission. Patients with OSA (apnoea-hypopnea index [AHI] ≥15 events/hour) were randomised 1:1 to CPAP treatment plus usual care (CPAP group) or usual care alone by a computerised system available 24 h/day. A group of patients with ACS but without OSA was also included as a reference group.

The patients received respiratory polygraphy and were stratified by their OSA: patients without OSA (n=596), those receiving usual care/poor CPAP adherence (n=978), and those with good CPAP adherence (n=229). The patients were followed for 1–5 years and blood pressure was measured at each office visit. About half of all patients (52%) had baseline hypertension.

After a median follow-up of 41 months, changes in blood pressure were similar between OSA and non-OSA groups. However, the research team observed an increase in blood pressure in the third tertile of the AHI (AHI >40 events/h) with a maximum difference in mean blood pressure of +3.3 mmHg at 30 months. OSA patients with good CPAP adherence (≥4 hours/night) had a reduced mean blood pressure after 18 months compared with usual care/poor CPAP adherence patients, a maximum mean difference of -4.7 mmHg (95% CI -6.7 to -2.7). In patients with severe OSA, there was a maximum mean difference of -7.1 mmHg (95% CI -10.3 to -3.8).

The researchers concluded that good CPAP adherence can mitigate the long-term increase in blood pressure observed in ACS patients with severe OSA.

1. Sánchez De La Torre M, et al. Long-Term Effect of OSA and CPAP on Blood Pressure in Patients with Acute Coronary Syndrome: A Post-Hoc Analysis of the ISAACC Study. Session C19, ATS International Conference 2022, San Francisco, CA, USA, 13–18 May.
2. [Sánchez-de-la-Torre M, et al. Ann Am Thorac Soc. 2022 Apr 20. Doi: 10.1513/AnnalsATS.202203-2600C.](https://doi.org/10.1513/AnnalsATS.202203-2600C)