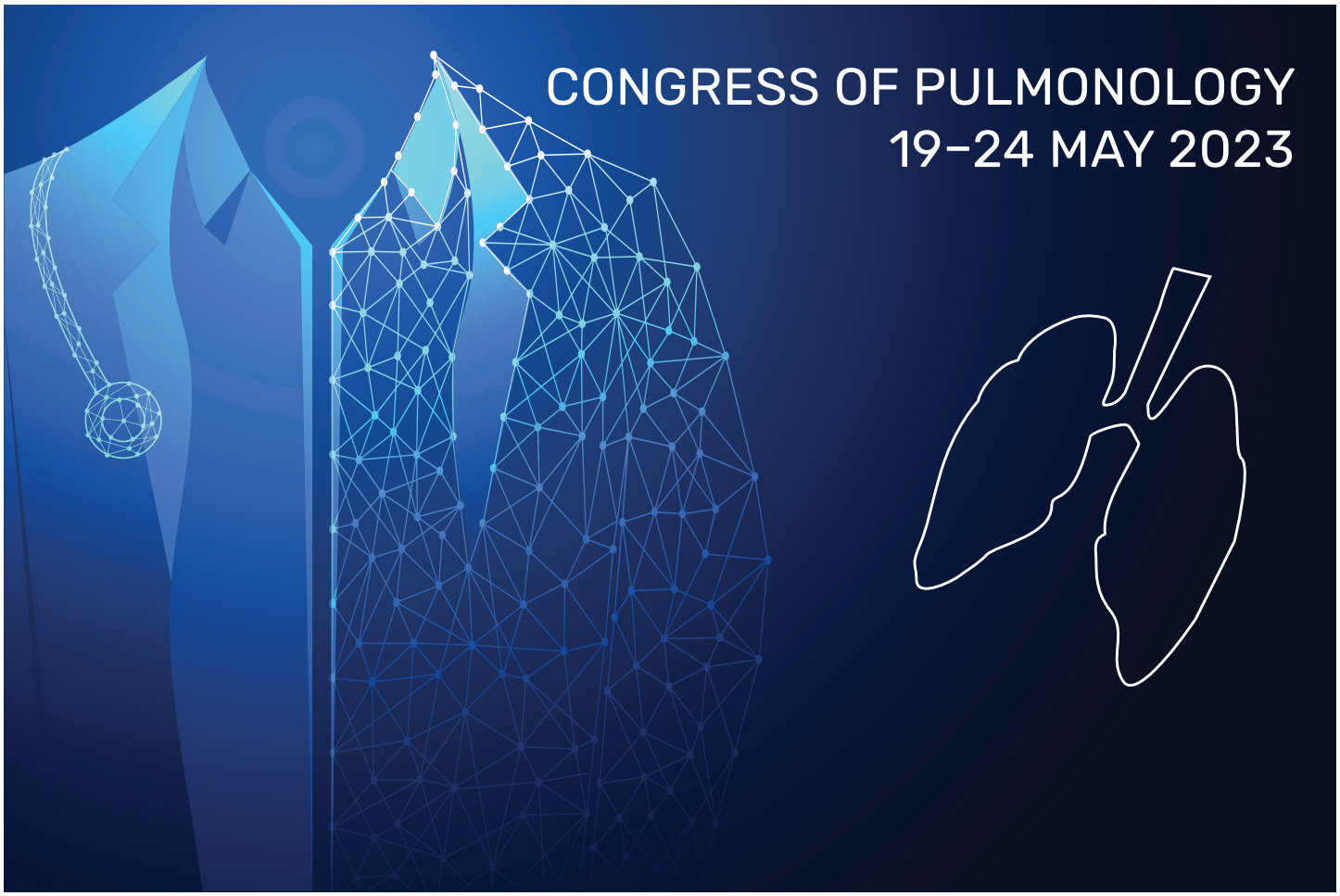
# ATS 2023 International Conference

American Thoracic Society




## Content

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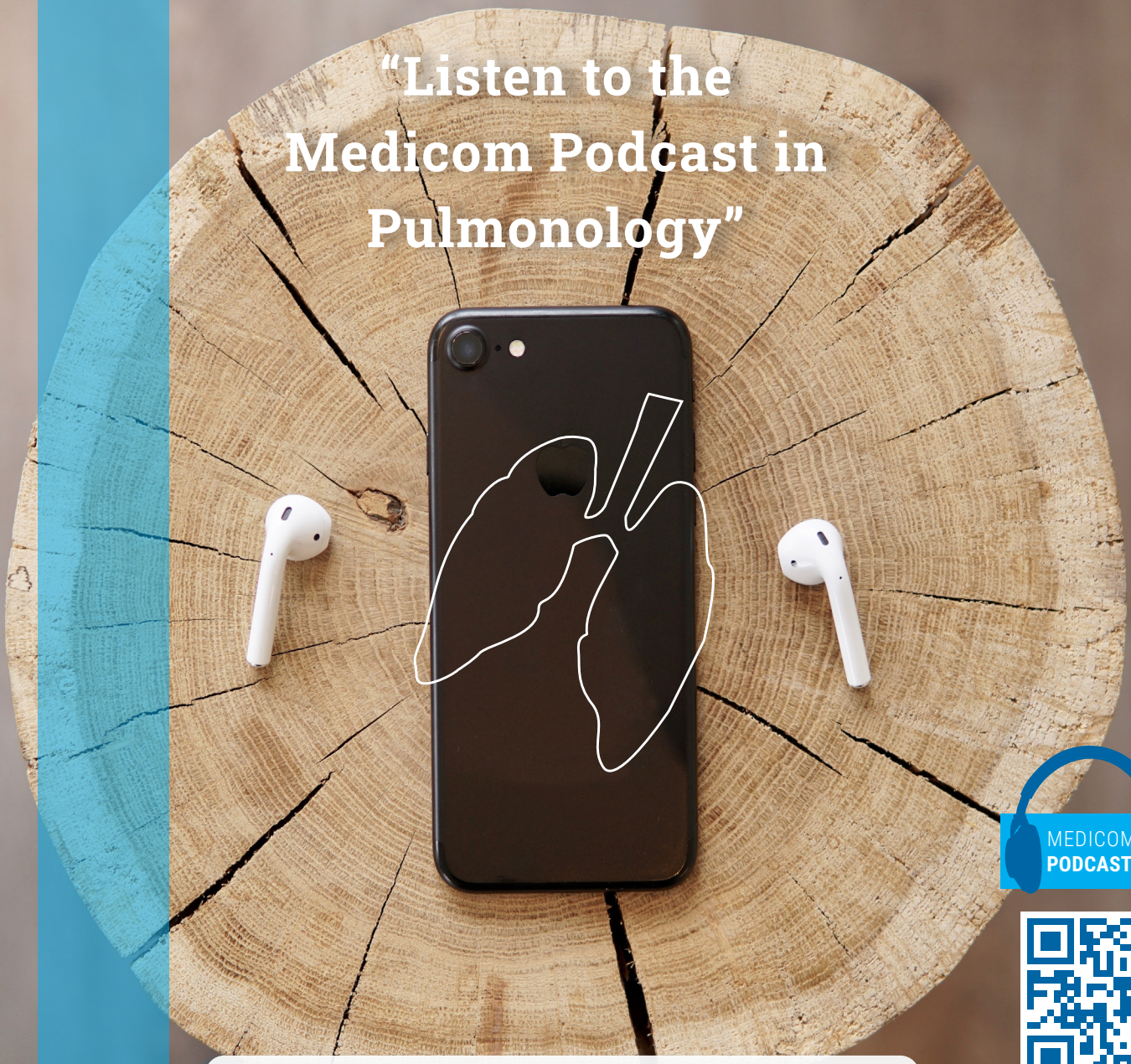

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# 1. Excellent results for C21 in idiopathic pulmonary fibrosis

**Patients with idiopathic pulmonary fibrosis (IPF) who were treated with the angiotensin type 2 receptor agonist C21 showed disease stabilisation over the 36-week study period of the phase 2a AIR trial. Together with the good tolerability of this agent and positive patient testimonials, the authors concluded that the results strongly support further investigation of C21 in a phase 2b study.**

The AIR (NCT00214526) trial assessed the safety and efficacy of C21 in 60 patients with IPF [1]. Dr Rohit Batta (Vicore Pharma, Sweden), who presented the data of the current interim analysis, emphasised that the baseline characteristics of the included patients were in line with other trials that included either treatment-naïve patients or patients that were not treated with the standard-of-care.

At 36 weeks, C21 displayed a significant positive impact on forced vital capacity compared with baseline (P<0.001). Dr Batta added that C21 was still efficacious if a 'worst-case-scenario' was wielded for the missing data (P<0.01). Importantly, C21 appeared to be a safe and tolerable agent. "There were no serious gastro-intestinal side effects," commented Dr Batta. "The only adverse event that occurred in >10% of the patients was hair loss, more frequently seen in the higher dose groups." He added that, compared with nintedanib, the safety profile of C21 looks promising.

Dr Batta concluded that the results of the AIR trial indicate that treatment with C21 is safe and may lead to disease stabilisation in patients with IPF.


1. Batta R, et al. An updated interim analysis of the Air trial: an open-label single-arm 36 week phase 2 trial of an angiotensin type 2 receptor agonist, C21, in individuals with IPF. Session A99, ATS International Conference 2023, 19–24 May, Washington DC, USA.


# 2. Can camlipixant improve quality of life of patients with refractory chronic cough?

**Both objective cough frequency and patient-reported cough severity improved significantly in patients with refractory chronic cough (RCC) if they were treated with camlipixant, results from the phase 2b SOOTHE trial demonstrated.**

Camlipixant is a selective P2X3 receptor inhibitor that is being tested as a potential therapy for patients with RCC. The SOOTHE trial (NCT04678206) randomised 249 patients to placebo (n=63) or to 1 of 3 dose groups of camlipixant; 12.5 mg, twice daily; 50 mg, twice daily; or 200 mg, twice daily [1]. "The primary outcome of 'change in objective cough frequency' was presented at last year's meeting," said Dr Lorcan McGarvey (Queen's University Belfast, UK) [2]. "However, we need to know whether the quality of life of patients with RCC improves if they are treated with camlipixant."

For this purpose, Dr McGarvey presented the outcomes of patient-reported cough severity, assessed by the cough severity visual analogue scale (VAS).

At day 15, all treatment groups demonstrated significant improvements in the cough severity VAS, with mean changes of -16.1 mm for the lowest dose group, -22.9 mm for the intermediate dose group, and -26.5 mm for the highest dose group, compared with a mean change of -3.7 mm for patients in the placebo group (P<0.001 for all). "The treatment effects appeared to become larger at Day 29," added Dr McGarvey. At day 29 namely, 44% of the patients in the highest dose group achieved a response rate ≥30 mm on the cough severity VAS, implying that this agent may instigate a clinically meaningful improvement in quality of life in a significant proportion of patients.

In conclusion, the SOOTHE trial displayed that camlipixant may have the potential to improve the objective cough frequency and the quality of life of patients with RCC.


1. McGarvey L, et al. Response in patient-reported cough severity in SOOTHE, a phase 2b trial of camlipixant in refractory chronic cough. Session A99, ATS International Conference 2023, 19–24 May, Washington DC, USA.
2. Smith J, et al. Am J Respir Crit Care Med. 2022;205:A5778.


# 3. Success for fluticasone furoate plus vilanterol in uncontrolled asthma

**Children between 5–17 years with uncontrolled asthma, taking inhaled corticosteroids, had a significantly improved forced expiratory volume in 1 second (FEV1) at 12 weeks if they were treated with fluticasone furoate plus vilanterol compared with fluticasone furoate alone.**

Dr Philippe Bareille (GSK, UK) presented the results from a global, randomised trial comparing treatment with inhaled corticosteroids plus a long-acting bronchodilator with treatment with inhaled corticosteroids alone in patients aged 5–17 years old with uncontrolled asthma on inhaled corticosteroids [1]. In total, 864 patients were randomised 1:1 to fluticasone furoate monotherapy or to fluticasone furoate plus vilanterol. Patients aged between 5 and 11 years (n=652) received 50 µg fluticasone furoate daily, whereas patients aged 12–17 received 100 µg of this agent on a daily base. The primary outcome was the weighted mean FEV1 (0–4 hours) at week 12.

The primary endpoint was met with an adjusted treatment difference of 0.083 L, favouring the combination arm over the monotherapy arm (95% CI 0.037–0.129). Similarly, both morning (adjusted treatment difference 6.2 L/min) and afternoon (adjusted treatment difference 8.2 L/min) peak expiratory flow (PEF) data showed a significant advantage of the combination regimen over the monotherapy regimen. In contrast, clinical outcome measures, such as 24-hour rescue-free periods or 24-hour symptom-free periods did not demonstrate a difference between the 2 treatment groups. Finally, the combination therapy was well tolerated, and the safety analysis did not reveal new safety issues.

"The combination of fluticasone furoate plus vilanterol improved the FEV1 of patients with uncontrolled asthma in a treatment cohort that included a large population of young patients," concluded Dr Bareille.

1. Bareille P, et al. A randomised, double-blind, parallel group, multicentre, stratified study evaluating the efficacy and safety of once-daily fluticasone furoate/vilanterol compared with once-daily fluticasone furoate in the treatment of asthma in participants aged 5-17 years old currently uncontrolled on inhaled corticosteroids. Session A13, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 4. TORREY trial: seralutinib associated with reduced pulmonary vascular resistance in PAH

**Seralutinib was associated with decreased pulmonary vascular resistance (PVR) in patients with pulmonary arterial hypertension (PAH). According to the authors, the encouraging results of the current phase 2 TORREY trial have instigated the initiation of a global phase 3 trial.**

"Seralutinib is a PDGFR, CSF1R, and c-KIT tyrosine kinase inhibitor that can be administered by dry powder inhalation," explained Prof. Robert Frantz (Mayo Clinic, MN, USA) at the start of his talk. The phase 2, randomised, double-blind, placebo-controlled TORREY trial (NCT04456998) examined the safety and efficacy of this agent in patients with PAH (n=86) [1]. The primary endpoint was the change in PVR from baseline after 24 weeks of therapy.

The primary endpoint was met, with a change in the least squares means of -74.9 dynes*s/cm$^5$ for patients receiving the experimental agent compared with +21.1 for patients receiving placebo, translating to a reduction in PVR of 14.3% (P=0.031). This reduction appeared to be larger in functional class III patients (20.8%; P=0.043). Prof. Frantz added that the observed reduction of PVR and an increase in pulmonary arterial capacitance (PAC), together with a reduction in NT-proBNP, indicates that the experimental agent seralutinib is decreasing the right ventricular afterload, favouring the conditions for the right side of the heart.

According to Prof. Frantz, seralutinib was well tolerated. The most frequently observed adverse events in the experimental arm were cough (43.2%), diarrhoea (13.6%), dizziness (11.4%), and nightmares (9.1%). Finally, there were 6 treatment-emergent adverse events that led to discontinuation in the seralutinib arm.

1. Frantz RP, et al. Seralutinib treatment in adult subjects with pulmonary arterial hypertension: results from the TORREY study. Session B13, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 5. Vitamin D for asthma protection: what is the optimal timing?

**High-dose prenatal and postnatal vitamin D intake appeared to be linked to a reduction of the occurrence of asthma or recurrent wheezing at 3 years of age, results from the VDAART study showed. Furthermore, those with sufficient prenatal and postnatal vitamin D intake were less likely to suffer from atopic asthma at the age of 6.**

"Studies have demonstrated that high dietary intake of vitamin D during pregnancy is associated with a reduced risk for asthma or recurrent wheezing in young children," said Dr Lourdes Ramirez (Brigham and Women's Hospital, MA, USA) [1,2]. "The effects of postnatal vitamin D intake on asthma protection are, however, less clear." Dr Ramirez and her colleagues aimed to answer the following questions:

- What is the optimal timing for vitamin D supplementation with regard to asthma protection?
- Do prenatal and/or postnatal vitamin D intake have a different influence on the occurrence of asthma?

The randomised Vitamin D Antenatal Asthma Reduction (VDAART) trial included 881 pregnant women at high risk for offspring asthma [2]. The primary outcome of asthma or recurrent wheezing at 3 years of age was compared between 4 exposure groups:

- High prenatal (4,400 IU per day) and postnatal (≥400 IU per day at the age of 12 months) vitamin D supplementation
- Low prenatal (400 IU per day) and postnatal (<400 IU per day) intake
- High prenatal and low postnatal intake
- Low prenatal and high postnatal intake

Infants who had received a sufficient intake of vitamin D, both prenatal and postnatal, had a numerically reduced risk of recurrent wheezing or asthma at age 3 compared with those who did not receive sufficient vitamin D intake, either prenatal or postnatal, but this result did not

reach statistical significance (aOR 0.51; 95% CI 0.24–1.08; P=0.08). Infants in the 'both' group had numerically improved odds ratios compared with those in the prenatal only (aOR 0.73; 95% CI 0.35–1.52) or postnatal only (aOR 1.04; 95% CI 0.50–2.15) group. In addition, atopic asthma at age 6, a secondary outcome measure, occurred less frequently in infants who received sufficient prenatal and postnatal vitamin D supplementation compared with those who did not (aOR 0.23; 95% CI 0.06–0.80; P=0.03).

According to Dr Ramirez, these results give some insight into the optimal timing of vitamin D supplementation with respect to asthma protection.


1. Wolsk HM, et al. PLoS One. 2017;12(10):e0186657.
2. Ramirez LG, et al. Association of prenatal maternal and infant vitamin D supplementation with offspring asthma outcomes. Session A13, ATS International Conference 2023, 19–24 May, Washington DC, USA.


## 7. Practice-changing results for ensifentrine in COPD

**In 2 phase 3 trials, ensifentrine significantly improved lung function, symptoms, and exacerbation rates in patients with GOLD class B COPD. The efficacy results were consistent across subgroups. Furthermore, ensifentrine was well tolerated and did not exceed placebo in terms of adverse event rates.**

"Ensifentrine has anti-inflammatory effects, provides mucociliary clearance, and is a bronchodilator," said Prof. Antonio Anzueto (University of Texas Health San Antonio, TX, USA). This agent was tested in the phase 3 ENHANCE-1 (NCT04535986) and ENHANCE-2 (NCT04542057) trials as an inhaled nebulised therapy for patients with GOLD class B COPD [1]. In the ENHANCE-1 trial, 300 patients were randomised to ensifentrine and 100 patients were randomised to placebo. Corresponding participant numbers in the ENHANCE-2 trial were 500 and 300, respectively. In both trials, the primary endpoint was the mean change from baseline forced expiratory volume in 1 second (FEV1) area under the curve (AUC) 0–12 hours at week 12.

In both trials, the primary endpoint was met. For the ENHANCE-1 trial, the mean change from baseline FEV1 AUC 0-12 hours was +87 ml (P<0.001). The corresponding result for the ENHANCE-2 trial was +94 ml (P<0.001). Prof. Anzueto mentioned that there were also improvements seen with regard to symptoms, quality of life, and the use of rescue medication. Importantly, the exacerbation rate reductions after 24 weeks for patients receiving ensifentrine were 36% and 43% for the ENHANCE-1 and ENHANCE 2 trials, respectively. Finally, the safety profile of ensifentrine was comparable with that of placebo, with serious treatment-emergent adverse event rates of 6–7% for the ensifentrine arms and the placebo arms.


1. Anzueto A, et al. Effect of ensifentrine, a novel PDE3 and PDE4 inhibitor, on lung function, symptoms, and exacerbations in patients with COPD: the ENHANCE trials. B13, ATS International Conference 2023, 19–24 May, Washington DC, USA.


## 8. Alvelestat for AATD meets primary endpoints in phase 2 trial

**In patients with alpha-1 antitrypsin deficiency associated lung disease (AATD-LD), treatment with the neutrophil elastase inhibitor alvelestat resulted in a reduction in blood neutrophil elastase activity, Aα-Val$^{360}$, and desmosine, which were the 3 primary endpoints of the phase 2 ASTRAEUS study.**

"Alvelestat is an oral, selective neutrophil elastase inhibitor, which may have some advantages over plasma-derived AAT, the current standard-of-care for patients with AATD-LD," mentioned Prof. Robert Stockley (University Hospital Birmingham, UK) at the start of his presentation. "It results in effective lung penetration and is resistant to oxidative inactivation," he clarified. The phase 2 ASTRAEUS study (NCT03636347) aimed to evaluate the effect of alvelestat on biomarkers of AATD-LD over 12 weeks [1]. The included patients were randomised to 1 of 2 doses of alvelestat, 120 mg, twice daily (n=22); 240 mg, twice daily (n=40), or to a placebo (n=36).

After 12 weeks of treatment, the change from baseline blood neutrophil elastase activity was significantly larger in the experimental groups than in the placebo group, displayed as the percentage change in the least squared means (LSM):

- Placebo: -18.1%
- Alvelestat 120 mg: -83.5%; P=0.001
- Alvelestat 240 mg: -93.3%; P<0.001

Also, a significant decrease in Aα-Val$^{360}$ was observed for the 240 mg group compared with placebo: % change from baseline LSM: placebo +11.7%; alvelestat 240 mg -22.7% (P=0.001). Similarly, a significant decrease in desmosine was reported for the 240 mg dose group: placebo +18.1%; alvelestat 240 mg -13.2% (P=0.041).


1. Stockley RA, et al. Alvelestat, an Oral Neutrophil Elastase Inhibitor in Alpha-1 Antitrypsin Deficiency (AATD): Results of a Phase II Trial. C15, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 9. Fewer exacerbations with dupilumab in COPD with type 2 inflammation

**In patients with COPD with type 2 inflammation, dupilumab significantly reduced the annualised exacerbation rate compared with placebo. Lung function tests and patient-reported outcomes confirmed the positive effect of dupilumab in this patient population.**

The phase 3 BOREAS trial (NCT03930732) randomised 939 patients with moderate to severe COPD with type 2 inflammation 1:1 to dupilumab or placebo [1]. The primary outcome was the annualised rate of moderate to severe exacerbations from baseline to week 52. Prof. Klaus Rabe (LungenClinic Grosshansdorf GmbH, Germany) presented the primary results of the trial, which were simultaneously published in the *New England Journal of Medicine* [2].

Although almost all patients were on triple therapy, dupilumab reduced the annualised exacerbation rate by 30% compared with placebo (0.78 vs 1.10; P<0.001). Prof. Rabe showed that this result was consistent across subgroups. Notably, at week 12 the change from baseline least squares means pre-bronchodilator forced expiratory volume in 1 second (FEV1) was 83 ml larger in the experimental group than in the placebo group (P<0.001), and this difference remained stable up to week 52. Similarly, patient-reported outcome measures displayed swift improvements after dupilumab therapy was initiated and these improvements stabilised over time.

In conclusion, on top of triple therapy, dupilumab was able to reduce the exacerbation rates in patients with COPD with type 2 inflammation in a large phase 3 trial.


1. Bhatt SP, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. B13, ATS International Conference 2023, 19–24 May, Washington DC, USA.
2. Bhatt SP, et al. NEJM. 2023; May 21. DOI: 10.1056/NEJMoa2303951.


## 10. New AATD therapy may alleviate treatment burden for patients

**A new investigational therapy for patients with alpha-1 antitrypsin deficiency (AATD) provided a longer duration of functional serum AAT than the duration that is usually seen for plasma-derived AAT, the standard-of-care for patients with AATD.**

"In patients with AATD, novel therapies that provide high levels of serum AAT with less frequent dosing are needed," said Dr Brooks Kuhn (UC Davis School of Medicine, CA, USA). INBRX-101 is a recombinant, next-generation human AAT Fc-fusion protein, designed to have a longer half-life and higher exposure than human plasma-derived AAT, which is the current standard of care for these patients. This investigational agent was evaluated in an open-label, dose-escalation phase 1 trial (NCT03815396) [1]. Dr Kuhn presented the results of the 'multiple ascending dose' part of the study, in which 31 participants with AATD received 3 times 3-weekly infusions of INBRX-101 (40, 80, or 120 mg/kg). Safety was the primary endpoint of the study.

"No patients had discontinued the study due to adverse events (AEs)," according to Dr Kuhn. The most common treatment-emergent AEs were fatigue (22.6%), increased blood pressure (12.9%), pruritus (9.7%), and urticaria (6.5%). "These were all grade 1 or 2 events that resolved in the same day with no to minimal supportive care," commented Dr Kuhn.

Furthermore, INBRX-101 showed a longer mean terminal elimination half-life (15.7–18.2 days) than that priorly observed for plasma-derived AAT (approximately 6 days). Also, measurable INBRX-101 exposure was reported across dose levels, up to 84 days after the third and final dose. Importantly, the 80 and 120 mg/kg INBRX-101 dose levels resulted in functional AAT levels that remained above the lower limit of normal during the 21-day dosing interval, and above the lower limit of normal after 28 days for the 120 mg/kg dose group after the third infusion. A phase 2 study is underway to further assess INBRX-101, 120 mg/kg, 3-weekly and 4-weekly, in patients with AATD (NCT05856331).


1. Kuhn BT, et al. Recombinant Human Alpha-1 Antitrypsin (AAT) Protein INBRX-101 Demonstrates Potential to Achieve Lung Penetration and Normal Functional Serum AAT Levels in Patients With AAT Deficiency. C15, ATS International Conference 2023, 19–24 May, Washington DC, USA.


## 11. Remarkable results for novel biologic therapy for asthma

**A novel biologic therapy targeting both TSLP and IL-13 swiftly and substantially reduced fractional exhaled nitric oxide (FeNO) in patients with asthma, suggesting that this agent, provisionally named SAR443765, inhibits airway inflammation and protects airway function in this group of patients.**

"NANOBODY molecules are a type of miniature, engineered antibodies, derived from Camelid heavy-chain only monoclonal antibodies," outlined Dr Benjamin Suratt (Sanofi, NJ, USA).

"SAR443765 is the first NANOBODY molecule in development for asthma." The drug candidate is a bi-specific monoclonal antibody which acts by targeting IL-13 and TSLP. To test this experimental biologic agent, Dr Suratt and co-investigators designed a double-blinded, placebo-controlled phase 1 trial in which 36 patients with mild-to-moderate asthma were randomised 2:1 to a single dose of SAR443765 or to placebo [1]. Safety and change from baseline FeNO at day 29 were the main outcomes of the study.

Compared with placebo, a single dose of SAR443765 resulted in a significant reduction in FeNO at day 29 (mean +0.8 ppb vs -39.1 ppb; P<0.1). At day 8, the reduction in FeNO in patients that received SAR443765 was already substantial (mean -33.0 ppb). Dr Suratt expressed that this reduction in FeNO appears to be much larger than the FeNO reductions that were reported in trials investigating TSLP inhibitors or IL-13 inhibitors. Furthermore, numerical improvements in lung function were observed for patients receiving SAR443765, despite the fact that these patients had close-to-normal lung functions at baseline. Finally, no serious adverse events were reported and the overall treatment-emergent adverse event rates were 75% in both arms of the study.

1. Suratt B, et al. Targeting of TSLP and IL-13 by the novel NANOBODY molecule SAR443765 reduces FeNO in asthma following single-dose exposure. B13, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 12. COVA trial: success for the investigational agent sarconeos in hospitalised COVID-19

**The COVA trial demonstrated sarconeos to be safe and efficacious in patients who were hospitalised for COVID-19, significantly reducing the risk of death or respiratory failure without increasing the risk for adverse events.**

Dr Girish Balachandran Nair (Beaumont Hospital, MI, USA) evaluated sarconeos, or BIO101, in hospitalised patients with COVID-19. "This agent activates the MAS receptor on the protective arm of the renin-angiotensin system (RAS), which may improve respiratory function," explained Dr Nair. In the phase 2/3 COVA trial (NCT04472728) that was initiated, 233 patients that were hospitalised due to a COVID-19 infection were randomised 1:1 to sarconeos or to placebo [1]. The primary endpoint was the proportion of patients who experienced respiratory failure or death from any cause at day 28.

The primary endpoint was met; patients who were treated with sarconeos experienced significantly fewer events of respiratory failure or all-cause mortality than patients who were treated with placebo, as assessed by Cochran-Mantel-Haenszel statistics (adjusted difference -11.4%; 95% CI -22.4 to -0.4; P=0.043). According to Dr Nair, these outcomes corresponded to a relative risk reduction of 44%. Furthermore, there was a trend towards a higher proportion of patients recovering or being discharged if they were treated with sarconeos instead of placebo (adjusted difference 11.0%; P=0.057). As for safety, fewer patients in the experimental arm experienced treatment-emergent adverse events (TEAE; 57.0% vs 64.4%) or serious TEAE (25.0% vs 30.8%). However, a larger proportion of patients in the sarconeos arm had increased gamma-glutamyl transferase (GGT) levels at day 28 (≥2 x baseline or ≥5 x upper limit of normal; 20.3% vs 12.5%).

1. Nair G, et al. COVA study: results from a double-blind, placebo-controlled phase 2/3 study to assess efficacy and safety of BIO101 in hospitalized COVID-19 patients. D95, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 13. Efficient detection of AECOPD with at-home vital signs monitoring

**Remote monitoring of vital signs in patients with COPD is effective with regard to the early detection of acute exacerbations (AE) of COPD (AECOPD). If acute exacerbations are detected early, therapeutical interventions and respiratory support can be supported swiftly, improving patients' quality of life.**

"Early detection of AECOPD is crucial to improve the quality of life and care for patients with COPD, and to reduce the economic burden of this disease," claimed Mr Yann Le Guillou (Biosency, France) [1]. "Although the annual risk of acute exacerbations is mainly determined by a patient's forced expiratory volume in 1 second (FEV1), exacerbation history, age, and smoking history, the daily risk is related to vital signs, dyspnoea, exposure to pathogens, and polluted environments." Mr Le Guillou argued that it is key to evaluate the daily risk in order to deliver appropriate treatments swiftly if needed. In the current study, including 8 patients with COPD, vital signs such as oxygen saturation (SpO2), heart rate, respiratory rate, and activity level were measured with an at-home device that delivered automated alerts to a monitoring pulmonologist. A patient-specific risk score, based on SpO2, heart rate, and respiratory rate, was used as a primary outcome measure.

During a total of 12,444 monitoring days, 1,500,000 measurements were collected, and 21 exacerbations were reported. The risk score algorithm predicted the occurrence of acute exacerbations with a specificity of 90.9% and a sensitivity of 85.7% (area under curve [AUC] 0.94), anticipating on average 3 days in advance of the upcoming exacerbation.

"There was a good performance in the detection of AECOPD in this study," concluded Mr Le Guillou. "Finally, I would like to address that it is important that remote patient monitoring is effortless for patients with COPD because it will lead to patient acceptation and high compliance rates."

1. Le Guillou Y, et al. Vital signs remote patient monitoring in real-life for early detection of AECOPD. C15, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 14. Improving quality care in sepsis through machine learning models

**Machine learning models, such as Random Forest, may be used to improve risk adjustment in patients with sepsis. Random Forest outperformed logistic regression analysis in providing a more accurate prediction of 90-day mortality in sepsis patients.**

A study by Dr Elizabeth Munroe (University of Michigan, MI, USA) aimed to assess risk-adjustment mortality models in patients with sepsis. "Traditional models do not fully incorporate acute physiology," she outlined. "Perhaps new machine learning models can do this better." The authors used data from the HMS-sepsis registry, including 5,303 cases of sepsis hospitalisation in 31 hospitals across Michigan [1]. The 90-day mortality rate of the sample was 27.0%. Several machine learning models were compared with a more traditional stepwise logistic regression model for the primary outcome of 90-day mortality. The models included patient characteristics, comorbidities, and parameters of acute physiology.

The stepwise logistic regression model had an area under the curve (AUC) of 0.77, whereas the best-performing machine learning model, Random Forest, had an AUC of 0.90. Dr Munroe explained that a disadvantage of the traditional model is its limited ability to assess interactions. In contrast, the more complex Random Forest model accounts for interactions. Furthermore, Radom Forest identified additional variables of importance for mortality in sepsis, such as creatinine and bilirubin levels, functional limitations, and dementia.

"Risk adjustment is important in sepsis quality care improvement," according to Dr Munroe. "This study showed that machine learning models may help to improve risk adjustment in this population. A next step may be to use the variables that were identified by machine learning models to improve our traditional model."

1. Munroe E, et al. Machine learning methods to address confounding in sepsis mortality rate. C94, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 15. Mitochondrial DNA levels predict COVID-19 severity

**Higher levels of plasma mitochondrial DNA at the time of hospital admission were associated with worse outcomes in patients with COVID-19. According to the authors, mitochondrial DNA levels can predict the severity of COVID-19 at an early stage. Implementing standard measurement of levels should be considered in clinical practice.**

"Mitochondrial DNA is an inflammatory mediator that is released during end-organ damage," said Dr Marlene Cano (Washington University in Saint Louis, MO, USA) [1]. The current, prospective study assessed whether mitochondrial DNA levels could predict COVID-19 severity in a relatively early stage of the disease (n=78). Mitochondrial DNA measures were performed on days 3, 7, 14, 21, and 84 after admission to the hospital. Mortality was the primary outcome of the study.

Mitochondrial DNA significantly predicted mortality in the current population of patients with COVID-19 (area under the curve [AUC] 0.73; 95% CI 0.58–0.88; P=0.0041). Similarly, mitochondrial DNA was a significant predictor of COVID-19 severity: higher plasma levels of mitochondrial DNA were associated with an increased risk for admission to the ICU, intubation, receiving vasopressors, and being supported with extracorporeal membrane oxygenation. Finally, Dr Cano added that tocilizumab was the only assessed therapy that appeared to reduce mitochondrial DNA levels in this population.

1. Cano M, et al. Mitochondrial DNA is an early predictor of COVID-19 severity of disease: validation cohort and response to targeted COVID-19 treatments. D95, ATS International Conference 2023, 19–24 May, Washington DC, USA.

## 16. Can information technology improve guideline adherence in sepsis care?

**A real-time monitoring and alerting system increased the delivery of guideline-recommended care for patients with suspected sepsis who were at risk for non-adherent care. The study did not, however, provide a signal that suggested that all-cause mortality could be improved following this intervention.**

"The Surviving Sepsis Campaign (SSC) guidelines and Center for Medicare and Medicaid Services (CMS) regulations recommend a bundle of interventions within

3 to 6 hours of sepsis recognition," said Dr Daniel Leisman (Massachusetts General Hospital, MA, USA) [1]. "However, adherence to these recommendations remains low." Dr Leisman evaluated whether real-time monitoring and automatic alerts may improve adherence to guideline interventions in patients with suspected sepsis who were at risk for non-adherent care. The included patients (n=1,377) were randomised to the intervention arm, in which an automated reminder page was sent to the physician if a 3-hour bundle element was not completed within 1 hour of the guideline time limit, or to the control group, in which the physicians did not receive automated alerts.

Clinicians ordered a significantly higher number of guideline-directed interventions for patients in the intervention arm than for patients in the control arm (adjusted OR 1.56; 95% CI 1.22–1.99; P=0.0004). As a result, more guideline-adherent care was delivered to patients in the intervention arm (adjusted OR 1.42; P=0.0099). However, there was no significant difference between the 2 study groups concerning mortality at day 28, ICU admissions, or the need for mechanical ventilation.

"Although the alerting system appeared to increase guideline-adherent care delivery in patients with suspected sepsis, this did not lead to a clear reduction in mortality," summarised Dr Leisman. "The high proportion of patients who discontinued antibiotic treatment early, or had negative cultures, highlights the difficulty in selecting the appropriate patients for sepsis bundle applications."

1. Leisman DE, et al. Effect of automated real-time feedback on early sepsis care: a pragmatic trial. C94, ATS International Conference 2023, 19–24 May, Washington DC, USA.