CHIEF SCIENTIST OFFICE

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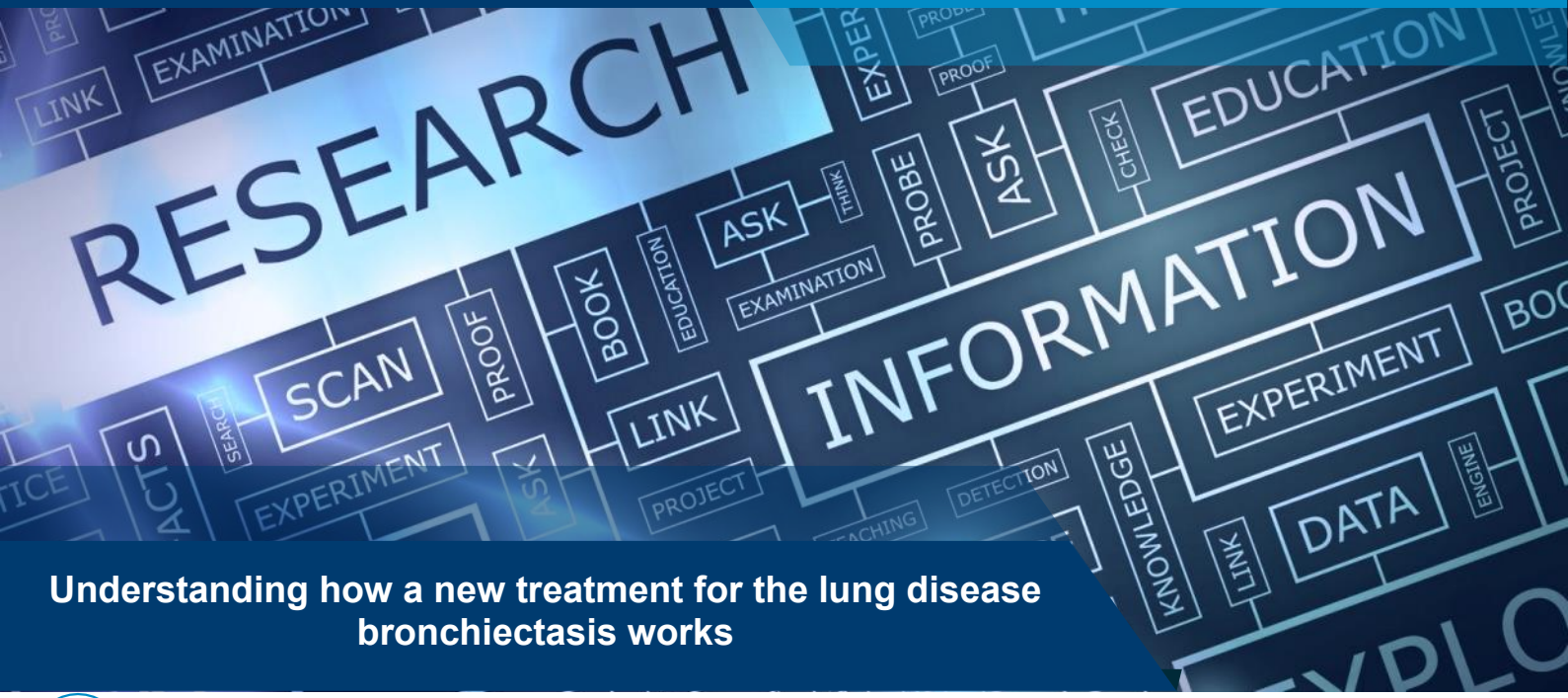
RESEARCH PROJECT BRIEFING



Understanding how a new treatment for the lung disease bronchiectasis works

AIMS

Brensocatib is a new drug that has been developed for the lung condition bronchiectasis. It is expected to be available in the UK in 2026. Bronchiectasis is a chronic inflammatory lung disease affecting over 300,00 people in the UK. People with bronchiectasis experience reduced quality of life due to symptoms of daily cough, mucus production and recurrent respiratory infections or 'exacerbations'. This ultimately leads to reduced lung function, and increased hospitalisations and mortality. Brensocatib is an anti-inflammatory drug that inhibits an enzyme called Dipeptidyl-peptidase 1 (DPP1). DPP1 activates proteases (cutting enzymes) contained within a type of white blood cell called neutrophils. When excessive amounts of these neutrophil proteases are released into the lungs they cause tissue damage and uncontrolled inflammation, leading to bronchiectasis progression. DPP1 inhibitors like brensocatib prevent activation of neutrophil proteases and could therefore reduce lung inflammation and improve the lives of people living with bronchiectasis. How these drugs impact lung inflammation is not yet known. In this study we aimed to:

- Aim 1: Study the effects of the DPP1 inhibitor brensocatib on markers of lung inflammation in patients with bronchiectasis taking part in a randomized clinical trial of brensocatib compared to placebo.
- Aim 2: Investigate whether parts of the immune system that change following treatment with DPP1 inhibitors can be used to predict which patients will benefit most from these drugs or could be targets for future treatments for bronchiectasis.

KEY FINDINGS

- Inhibiting DPP1 with brensocatib has broad anti-inflammatory effects in people with bronchiectasis.
- People with bronchiectasis taking DPP1 inhibitors had a more effective immune response as measured by inflammatory markers in the lungs. Other findings suggested improved defense against infections (due to increases in proteins that fight bacteria and viruses), and reduced mucins (a primary component of mucus) suggesting potential to reduce chronic mucus symptoms.
- Markers of treatment response to brensocatib were identified, to guide clinical use of DPP1 inhibitors.

WHAT DID THE STUDY INVOLVE?

Part 1

We measured how levels of proteins involved in inflammation changed in the lungs of patients with bronchiectasis after treatment with the DPP1 inhibitor brensocatib. To do this we used sputum (airway mucus) samples from participants in the WILLOW phase II randomized controlled trial of brensocatib (NCT 03218917). In this trial, bronchiectasis patients received either 10mg brensocatib, 25mg brensocatib or placebo tablets once daily for 24 weeks. We used sputum samples collected at baseline (start of treatment), week 4 of treatment, week 24 (end of treatment), and week 28 (4 weeks after treatment finished).

To get a good picture of the wider effects of DPP1 inhibitors on features of bronchiectasis we measured the following markers:

- Proteins that contribute to lung inflammation: Azurocidin-1 (AZU1)
- Anti-microbial peptides (proteins that fight bacteria and viruses and may protect against respiratory infections): secretory leukoproteinase inhibitor (SLPI) and α-defensin-3 (DEFA3).
- Proteins that contribute to excessive mucus in the lungs: Mucin-5AC (MUC5AC)
- Forty-five immune signals called cytokines that give clues to broader effects on the immune system.

Part 2

We confirmed the relationship between DPP1 inhibitors and these immune system changes by showing how the proteins changed by brensocatib were related to changes in neutrophil elastase (NE). NE is a key neutrophil protease known to contribute to excessive inflammation in bronchiectasis that is reduced by DPP1 inhibitors. We measured the above markers and compared them to NE levels in sputum from the pan-European BRIDGE (Bronchiectasis Research Involving Databases, Genomics and Endotyping) bronchiectasis cohort study (NCT 03791086).

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Biomarker response to treatment in the WILLOW trial:

- Patients receiving brensocatib 10mg or 25mg had fewer respiratory exacerbations compared to placebo treated patients. We investigated whether this was related to changes in the lungs using sputum samples.
- At week 4 and week 24 of treatment, the pro-inflammatory protein AZU1 had significantly reduced in the 10 and 25mg brensocatib groups compared to placebo suggesting reduced lung inflammation (Figure 1.A).
- By week 4 and 24 of treatment the anti-microbial peptides DEFA3 and SLPI were significantly increased in both treatment groups compared to placebo suggesting improved lung defense against airway infections (Figure 1. B and C). By week 24 of treatment, MUC5AC, which is a primary component of mucus, was significantly reduced in the 25mg treatment group compared to placebo, suggesting reduced airway mucus (Figure 1.D).
- These results show inhibiting DPP1 likely affects both respiratory exacerbations and chronic symptoms in bronchiectasis by reducing inflammation, improving defense against infection and improving clearance of mucus.

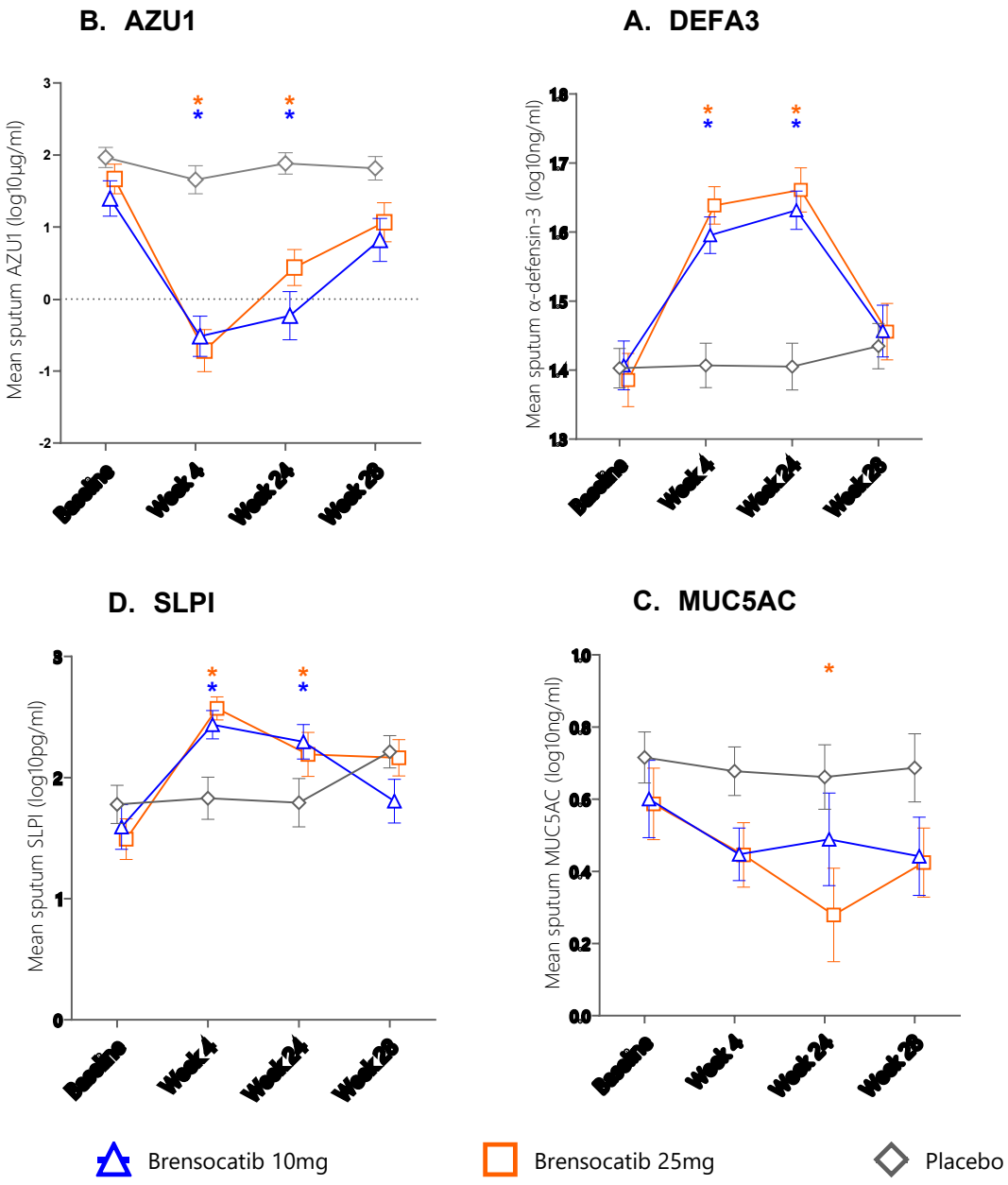


Figure 1. The level of proteins at each of the four time points measured within the WILLOW trial by treatment group showing: A. reduced AZU1, B. increased DEFA3, C. increased SLPI and D. reduced MUC5AC in those on treatment compared to those on placebo.

Of the 45 cytokines measured in patient sputum, 15 cytokines (Figure 2) were significantly increased by brensocatib, many of which are involved in fighting viral infections and resolving inflammation. These results further suggest inhibiting DPP1 enhances the immune response in the lungs which may help with reducing inflammation and fighting against infections. Neutrophil proteases including NE have been reported to damage and degrade most of the cytokines observed to increase with treatment. Therefore, it is likely levels of these cytokines increase because brensocatib reduces neutrophil proteases which would have otherwise destroyed them.

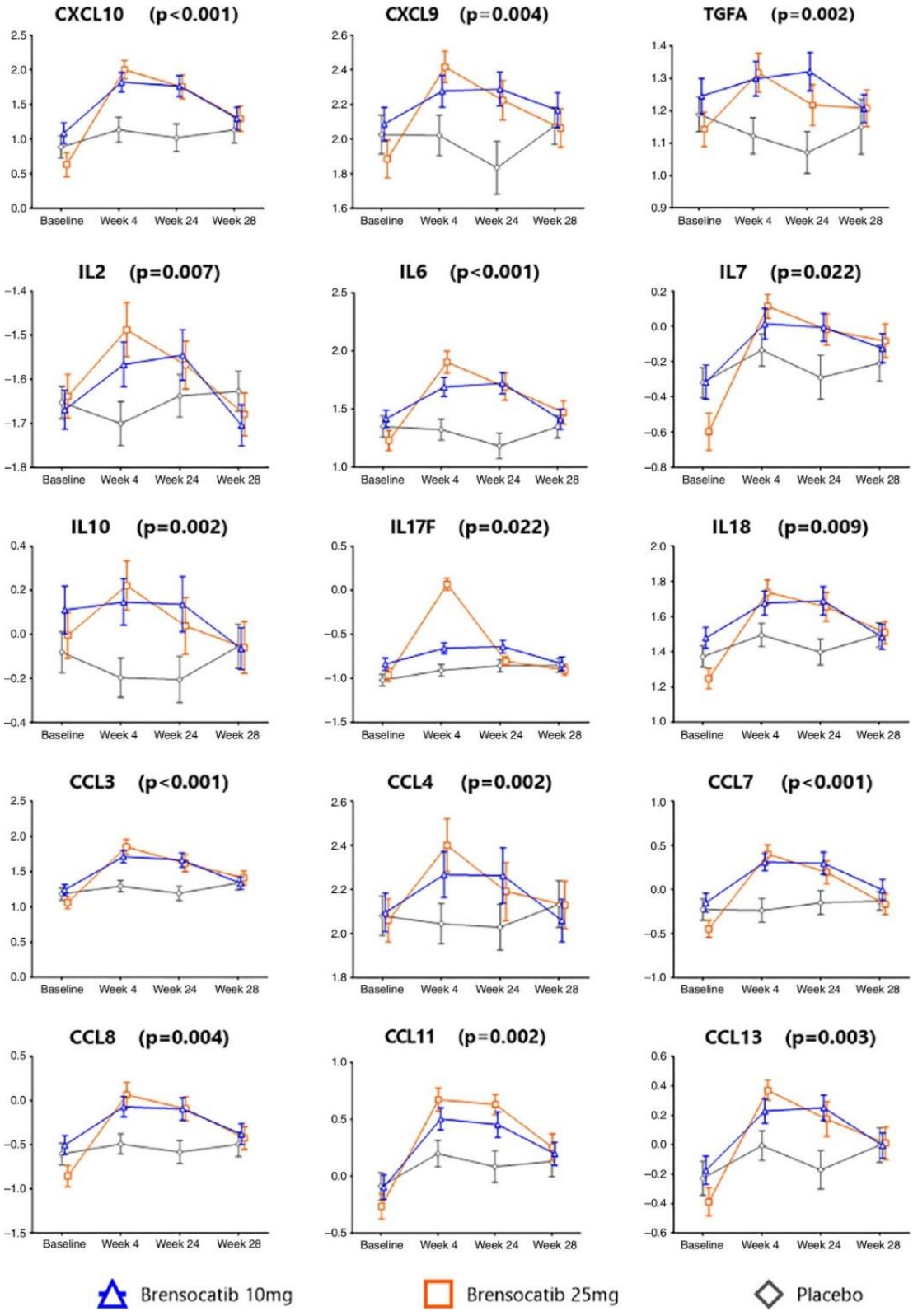


Figure 2. The level of cytokines at each of the four time points by treatment group for the 15 cytokines affected by brensocatib, showing all 15 increased by week 4 of treatment in both treatment groups compared to placebo and stayed high till week 24 (end of treatment) before returning to placebo levels by 4 weeks after treatment ended.

BRIDGE Validation cohort

To investigate the relationship between NE, the main neutrophil protease reduced by brensocatib, and the inflammatory proteins and cytokines which were changed by brensocatib treatment, all markers were measured in the BRIDGE bronchiectasis cohort study and correlated with NE activity (Figure 3). The majority of markers increased by brensocatib (shown in red), were inversely correlated with NE activity, meaning the higher the NE activity, the lower the levels of these markers.

These results further strengthen the conclusion from the previous findings in the WILLOW trial that DPP1 inhibitors protect the airways by increasing levels of these protective markers through inactivating harmful neutrophil proteases such as NE which would have otherwise destroyed them. This further confirms the beneficial effects of reducing neutrophil proteases using brensocatib on the overall immune response.

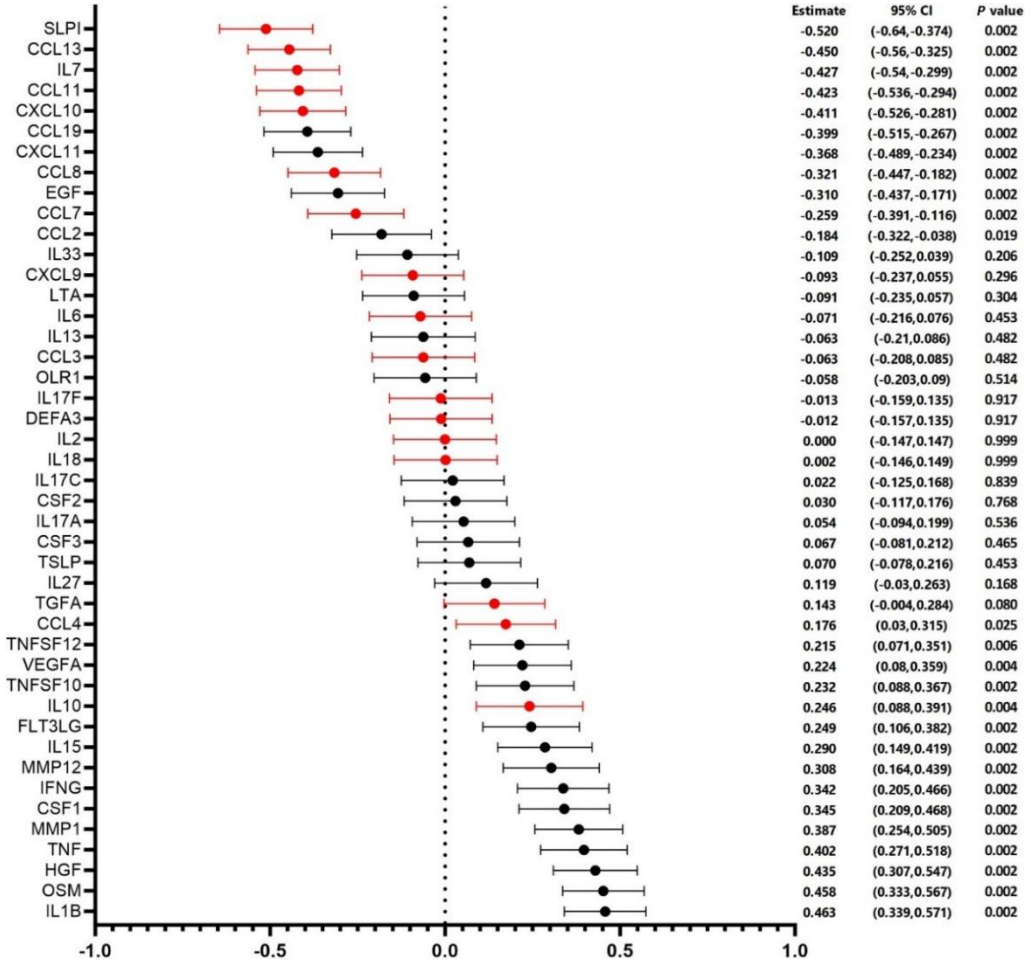


Figure 3. Correlations between NE activity and all markers measured in the BRIDGE samples. Markers that were increased after treatment with brensocatib are shown in red. The majority of these were negatively correlated with NE activity suggesting higher levels of NE lead to greater destruction of these markers.

WHAT IMPACT COULD THE FINDINGS HAVE?

Bronchiectasis is a complex disease, and patients suffer from airway inflammation, infection and excess mucus production. These results show that DPP1 inhibition has broad effects and can target each of these disease components. The result is a reduction in exacerbations and an improvement in quality of life for people with bronchiectasis.

Brensocatib treatment for bronchiectasis has shown positive results in phase II and III clinical trials and is set to become the first approved treatment for bronchiectasis, available as early as 2026 These results help doctors in Scotland and across the world prescribing the treatment to understand more about the way it works meaning they will be able to identify patients who may benefit, and help these patients understand how this treatment may improve their symptoms. Furthermore, these results highlight a broad treatment effect which means brensocatib may also be effective in other inflammatory conditions where neutrophil proteases play a role. These could include chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis to name but a few, meaning potentially improved quality of life for a wider group of patients across Scotland and beyond.

Finally, these results identified markers that could be used to measure treatment response in patients receiving brensocatib. This is useful in clinical practice to ensure each individual patients receiving the most effective treatment for them for both bronchiectasis and other inflammatory conditions.

HOW WILL THE OUTCOMES BE DISSEMINATED?

These results have been published in the high impact American Journal of Respiratory and Critical Care Medicine (ARJRCCM) journal:

Johnson, E.D., Long, M.B., Perea, L., Shih, V.H., Fernandez, C., Teper, A., Cipolla, D., McIntosh, E., Galloway, R., Eke, Z., Shuttleworth, M., Hull, R., Arietta Spinou, Soyza, A.D., Ringshausen, F.C., Pieter Goeminne, Lorent, N., Haworth, C., Loebinger, M.R. and Blasi, F. (2025). Broad Immunomodulatory Effects of the Dipeptidyl-peptidase-1 Inhibitor Brensocatib in Bronchiectasis: Data from the Phase 2, Double-Blind, Place-controlled WILLOW Trial. American Journal of Respiratory and Critical Care Medicine. doi:https://doi.org/10.1164/rccm.202408-1545oc.

These results were presented at the British Thoracic Society (BTS) winter meeting 2024 as part of the British thoracic society/British association for lung research (BALR) early career research award presentation.

These results were also presented to the Tayside bronchiectasis support group whose input at the beginning of the project helped shape the research questions. Results were also posted on Twitter and the University of Dundee website to engage with the broader public.

Based on the results of this study AZU1 is already being used as a biomarker in pediatric trials of DPP1 inhibitors. Several other biomarkers including SLPI are also being investigated as treatment targets in bronchiectasis.

CONCLUSION

This study showed that DPP1 inhibition with brensocatib in bronchiectasis patients has broad effects targeting inflammation, immune defense and clearance of mucus. Furthermore, these results suggest these broad anti-inflammatory effects are related to direct reduction of neutrophil proteases such as NE. As well as providing important insights into the mechanisms by which DPP1 inhibitors reduce exacerbations and improve symptoms in bronchiectasis, this study identified potential new markers of treatment response, which could be used to ensure this anti-inflammatory treatment is used effectively by doctors to improve the lives of patients with bronchiectasis.

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