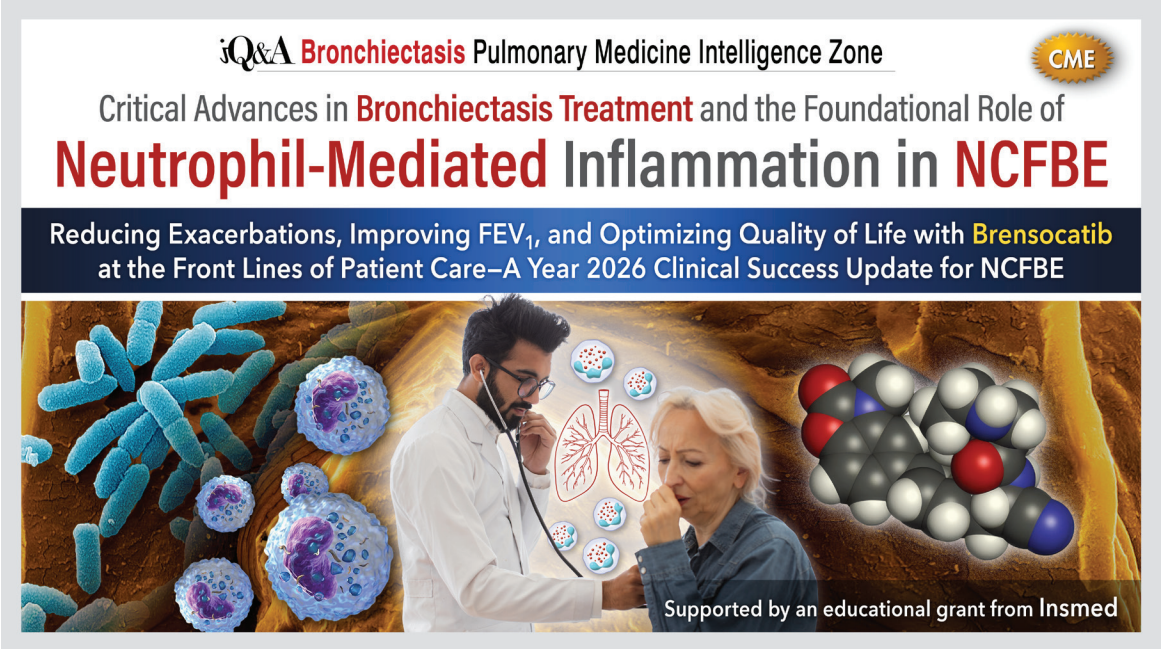
Critical Advances in Bronchiectasis Treatment and the Foundational Role of

Neutrophil-Mediated Inflammation in NCFBE

Reducing Exacerbations, Improving FEV1, and Optimizing Quality of Life with Brensocatib

Clinical Success Update for the Pulmonary, Respiratory, Infectious Disease, and Primary Care Specialist



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Professor James Chalmers

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QUESTION # 1: Professor Chalmers, can you share with us your clinical and investigational interest in identifying new, approved therapeutic strategies for non-cystic fibrosis bronchiectasis, and what you plan to cover in this iQ&A Bronchiectasis Pulmonary Medicine Intelligence Zone?

QUESTION # 2: Can you discuss the current burden of NCFBE for patients and the healthcare system, in general, especially in regions globally—U.S., Europe, and Japan—where we see high disease burden, increasing prevalence, and profoundly impaired quality of life?

QUESTION # 3: Are we witnessing a new therapeutic era for NCFBE—in particular, the recent approval of medications such as brensocatib that has been developed to target the underlying neutrophil-mediated inflammation that undergirds the pathobiology of this condition?

QUESTION # 4: Given that NCFBE is a heterogeneous and global disease, what are its underlying etiologies—especially chronic infection— and how does the recognition of these precipitating factors help improve detection, treatment, and confirmation of this frequently devastating pulmonary condition?

QUESTION # 5: What are the underlying pathobiological processes—immune-related, neutrophil-related, neutrophil serine protease-related, cytokine-related—that are primarily responsible for the progressive destruction of lung tissue that underpin the clinical symptoms and natural history of NCFBE?

QUESTION # 6: Given that NCFBE is primarily a progressive disease of inflammatory dysregulation, can you discuss why, until now with the approval of brensocatib, the previous toolkit was inadequate for achieving therapeutic responses that would significantly improve patient outcomes?

QUESTION # 7: How has our delineation of the role of the neutrophil-mediated chronic inflammation in NCFBE changed the approach to developing and validating new disease-modifying treatments?

QUESTION # 8: Can you discuss the mechanistic role of neutrophil serine proteases (NSPs) as mediators of inflammation in NCFBE and the role of inhibition of DPP-1 with brensocatib as a potential mechanism-of-action (MOA) for reducing NSPs and their effect on progressive pulmonary inflammation?

QUESTION # 9: Before even discussing the WILLOW and ASPEN trials, can you discuss what specific clinical biomarkers and symptomatic end points you and your colleagues felt were essential to include in order to fully characterize this brensocatib's effectiveness and potential impact on disease modification and quality of life?

QUESTION # 10: Can you discuss the trial design and results of the Phase 2 WILLOW study which evaluated the efficacy and safety of brensocatib across multiple clinical endpoints in persons with NCFBE? Specifically, what endpoints were measured? Did brensocatib improve quality of life in trial participants with NCFBE?

QUESTION # 11: Given the results seen with brensocatib in persons in with NCFBE in the WILLOW trial, what positive signals and endpoints—reduced frequency of exacerbations, improved quality of life, reduced reliance on antibiotics—in that trial did you want to expand on in the Phase 3 trial, ASPEN?

QUESTION # 12: Can you discuss the trial design and results of the Phase 3 ASPEN study? What new information, including the differential effects of your two dosing regimens (10mg and 25mg) about the relative efficacy and safety of brensocatib were you able to explore in more detail??

QUESTION # 13: Because the ASPEN trial did demonstrate significant and clinically meaningful differential efficacy between the 10mg and 25mg dose of brensocatib, how would you recommend clinicians respond to these trial-based findings and translate their implications to dosing at the front lines of NCFBE management?

QUESTION # 14: Against the positive results of the ASPEN trial, in combination with the FDA approval of brensocatib, can you share how to best identify specific patient populations who are likely to benefit from the disease- and symptom-modifying effects of this novel, inflammation-mediating therapy?

QUESTION # 15: Upon starting therapy with brensocatib, what are the first signs of clinical improvement that patients with NCFBE are likely to report to their treating physicians? What endpoints—symptomatic and spirometry—should be monitored?

QUESTION # 16: Given that you and other specialists in the field of NCFBE and pulmonary/respiratory medicine have identified brensocatib as a critical, exciting breakthrough treatment, how do you see its role in the present and near future management of persons with NCFBE?

Prof. Francesco Blasi, MD, FERS

Professor of Respiratory Medicine
Department of Pathophysiology and Transplantation,
Vice Rector for Relations with the National Health Service
University of Milan
Dean of the School of Medicine, University of Milan
Milan, Italy

QUESTION # 17: Professor Blasi, can you kindly introduce yourself and share with us your role at the University of Milan and, more specifically, your clinical and investigational interests in non-cystic fibrosis bronchiectasis?

QUESTION # 18: Can you explain the importance of neutrophil-mediated inflammation as a primary driver of the pathobiology of NCFBE, and the implications of new therapeutic approaches that mitigate the destructive effects of this progressive process?

QUESTION # 19: What are the necessary symptomatic, historical, and radiographic criteria that confirm the diagnosis of NCFBE and how do we improve our clinical strategies to ensure early identification of persons with NCFBE so they can become eligible for treatment?

QUESTION # 20: Can you discuss the mechanism of action of DPP-1 inhibitors such as brensocatib and what clinical triggers and associated findings would provide rationale for treating patients with confirmed NCFBE with this new class of agents?

QUESTION # 21: What aspects of the trial designs for ASPEN and WILLOW are most informative in terms of helping clinicians identify persons with NCFBE who are likely to benefit from brensocatib and, by extension, provide an evidence-driven roadmap for monitoring these patients on treatment?

QUESTION # 22: With the understanding that the WILLOW and ASPEN trials evaluated both 10mg and 25mg daily doses of brensocatib, how do you interpret the findings and apply the FEV1 improvement results that were observed in the higher dose treatment arms?

QUESTION # 23: Given the side effects and compliance profiles with brensocatib, and that we now have a medication that targets a critical pathobiological process in NCFBE—neutrophil-mediated inflammation—who are the ideal candidates for this novel therapy?

QUESTION # 24: Can brensocatib be used in both patients who have new onset NCFBE as well as in older patients who have longstanding NCFBE with poor prognostic factors? Did subgroup analyses from ASPEN or WILLOW provide any direction regarding this question?

QUESTION # 25: Can summarize for the clinical pulmonary, infectious disease, and primary care specialist what you see as the current evidence-based role and importance of brensocatib in the treatment of NCFBE?

Professor Michael Loebinger, MA, FRCP, PhD

Director of the Lung Division
Clinical Director of Laboratory Medicine
Deputy Medical Director
Consultant Respiratory Medicine
Royal Brompton & Harefield Hospitals
Professor of Practice (Respiratory Medicine)
National Heart and Lung Institute
Imperial College London
London, United Kingdom

QUESTION # 26: Professor Loebinger, can you kindly introduce yourself and share with us your role at the Royal Brompton & Harefield Hospitals? And, what you plan to cover in this landmark iQ&A Bronchiectasis Pulmonary Medicine Intelligence Zone?

QUESTION # 27: Can you discuss the current burden of NCFBE for patients and the healthcare system, in general, especially in regions globally—U.S., Europe, and Japan—where we see high disease burden, increasing prevalence, and profoundly impaired quality of life?

QUESTION # 28: With respect to targeting therapy at neutrophil-mediated inflammation, how does our understanding of the underlying pathobiology help select among treatment options that frequently require multi-modal approaches?

QUESTION # 29: Can you discuss what systematic approach you apply to confirming the diagnosis of NCFBE?

QUESTION # 30: What are the infectious etiologies that undergird NCFBE and how does documentation of these pathogens affect treatment decisions for this disease state?

QUESTION # 31: Against the backdrop of these multiple infectious agents that play an important, exacerbating role in NCFBE, what other underlying processes—in particular, neutrophil-mediated inflammation and serine proteases—play an equally foundational role in NCFBE exacerbations and disease progression?

QUESTION # 32: Given the results and outcome improvements seen with brensocatib in WILLOW, what positive signals and end points—among them, reduced frequency of exacerbations, improved quality of life, reduced reliance on antibiotics, decreases in FEV1 and so on—were confirmed in ASPEN?

QUESTION # 33: From your perspective as an investigator in the brensocatib trials, what do you feel are the most important translation take-aways about the deployment of this novel neutrophil-and-inflammation-targeting therapy at the front lines of NCFBE care?

Professor Kevin Winthrop, MD, MPH

Professor of Infectious Diseases, Ophthalmology,
Professor of Public Health and Preventive Medicine (joint appointment),
Division of Infectious Diseases, OHSU
Oregon Health and Sciences University
Portland, Oregon, USA

QUESTION # 35: Professor Winthrop, can you kindly introduce yourself and share with us your role at Oregon Health Sciences University? And what you plan to cover in this landmark iQ&A Bronchiectasis Pulmonary Medicine Intelligence Zone?

QUESTION # 36: Can you discuss the current burden of NCFBE and the unmet need for the healthcare system? How do we address high disease burden, increasing prevalence, and profoundly impaired quality of life in NCFBE?

QUESTION # 37: Given that NCFBE is a heterogeneous and global disease, what are its underlying etiologies—especially chronic infection— and how does the recognition of these precipitating factors and endotypes help improve detection, treatment, and confirmation of this frequently devastating pulmonary condition?

QUESTION # 38: What are the non-negotiable features, symptoms, test results, and findings that confirm the diagnosis of NCFBE and, by extension, therefore make persons potential candidates for inflammation-targeting therapy with such drugs as brensocatib?

QUESTION # 39: Given that the side effects and compliance profiles, and that we now have a medication that targets neutrophil-mediated inflammation, who are the ideal candidates for this novel therapy and how should specialists select persons with NCFBE for long term treatment?

QUESTION # 40: Even with the introduction of new inflammation-reducing agents such as brensocatib, what do you envision will be the role of antibiotics as a mainstay in the NCFBE toolkit?

QUESTION # 41: Can you explain the importance of neutrophil-mediated inflammation as a primary driver of the pathobiology of NCFBE, and the implications of therapeutic approaches that mitigate the effects of this progressive process across the heterogeneous spectrum?

QUESTION # 42: What aspects of the trial designs for ASPEN and WILLOW do you feel are most informative in terms of helping clinicians identify persons with NCFBE who are likely to benefit from brensocatib; and, by extension, provide an evidence-driven roadmap for monitoring these patients?

QUESTION # 43: Please discuss the trial design and results of the ASPEN and WILLOW trials. And specifically, what aspects of the trial designs for these studies do you feel are most informative in terms of helping clinicians identify persons with NCFBE who are likely to benefit from brensocatib; and, by extension, provide an evidence-driven roadmap for monitoring these patients?

QUESTION # 44: Given the statistically significant improved FEV1 outcomes in of the 25mg vs 10mg dose of brensocatib, and virtually equivalent side effect profiles of the two dosing regimens, how do you use the data to guide your use, dose-wise, of brensocatib?

QUESTION # 45: Given the results of the WILLOW and ASPEN trials, how do you recommend we identify those persons with documented NCFBE who represent ideal candidates for this therapeutic approach?

QUESTION # 46: How should clinicians monitor the success, or lack of success, of brensocatib therapy, once a patient has been committed to this treatment?

QUESTION # 47: How are brensocatib and other investigational drugs in the pipeline shaping/changing the multimodal treatment landscape for NCFBE?

Anne E. O'Donnell, MD

The Nehemiah and Naomi Cohen Chair in Pulmonary Disease Research
Professor of Medicine
Interim Chair, Department of Medicine
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Georgetown University Medical Center/Medstar Georgetown University Hospital
Washington, DC, USA

QUESTION # 48: Professor O'Donnell, can you kindly introduce yourself and your role at Georgetown University Medical Center, and share with us your interest in identifying new, approved therapeutic strategies for NCFBE?

QUESTION # 49: What does the current toolkit look like for NCFBE? What are its strengths and weaknesses, especially as it relates to the "inflammatory vortex" that undergirds the pathobiology of this condition; and, by extension, what are the unmet needs for achieving better clinical outcomes?

QUESTION # 50: What is the data- and science-driven rationale for focusing on neutrophil-mediated inflammation as a pathobiological target—in addition, let's say to infectious pathogens—for managing NCFBE?

QUESTION # 50: We are witnessing a new therapeutic era for NCFBE—in particular, the recent approval of medications such as brensocatib that has been developed to target the underlying neutrophil-mediated inflammation that undergirds the pathobiology of this condition? How have the WILLOW and ASPEN trials helped move the needle?

QUESTION # 52: What, in your assessment, were the most significant primary and secondary end points achieved in the ASPEN trial evaluating the safety and efficacy of brensocatib in NCFBE?

QUESTION # 53: Against the backdrop of approval for brensocatib by the FDA in patients with bronchiectasis, what are the criteria and features you use to identify persons with NCFBE whom you feel represent ideal therapeutic candidates for this inflammation-targeting medication?

QUESTION # 54: Are there patients who, by virtue of having adverse prognostic features for NCFBE, you would consider highly amenable candidates for brensocatib therapy? How should this novel treatment fit into our clinical care model?

QUESTION # 55: Once you start a patient on brensocatib, what should you see in a patient who is responding well to this therapy? And how long does it take to confirm drug effectiveness?

QUESTION # 56: Once you commit a patient to brensocatib, how do you follow therapeutic progress? Do you use biomarkers? Other monitoring strategies?

QUESTION # 57: In what ways does the introduction of brensocatib into the multi-modal toolkit for NCF represent an important clinical advance and based on the WILLOW and ASPEN trials—as well as the FDA label—how do you see the role of this new inflammation-mitigating DPP-1 (neutrophil elastase) inhibitor for management of NCFBE?

Professor David E. Griffith, MD

Professor of Medicine
National Jewish Health
Denver, Colorado, USA

QUESTION # 58: Professor Griffith, can you kindly introduce yourself and your role at National Jewish Health, and share with us your clinical and investigational interest in identifying new, approved therapeutic strategies for non-cystic fibrosis bronchiectasis (NCFBE) , and what you plan to cover in this landmark iQ&A Bronchiectasis Pulmonary Medicine Intelligence Zone?

QUESTION # 59: Can you discuss the current burden of NCFBE and the significant unmet need for the healthcare system? How do we address high disease burden, increasing prevalence, and profoundly impaired quality of life in NCFBE, all of which are complicated by suboptimal recognition?

QUESTION # 60: What are the consensus- and guideline-adherent recommendations for confirming the diagnosis of NCFBE? And what risk stratification tools might apply that would be useful when considering targeting neutrophil-mediated inflammation?

QUESTION # 61: How does the complexity and heterogeneity of NCFBE—with underlying inflammatory and infectious precipitants—affect selection of specific therapeutic agents that might be used as part of multi-modal therapy?

QUESTION # 62: We now understand that infectious triggers of architectural destruction of bronchial tissues is further potentiated by chronic and dysregulated inflammatory processes mediated by neutrophil serine proteases, producing a "vicious vortex." How does this evolving paradigm shape our new treatment roadmap for NCFBE?

QUESTION # 634: What aspects of the trial designs for ASPEN and WILLOW do you feel are most informative in terms of helping clinicians identify persons with NCFBE who are likely to benefit from brensocatib; and, by extension, provide an evidence-driven roadmap, including 10mg vs 25mg daily dose selection?

QUESTION # 64: Given the results of the WILLOW and ASPEN trials, and the broad FDA label for brensocatib, how do you recommend we identify those persons with documented NCFBE who represent ideal candidates for this therapeutic approach?

QUESTION # 65: How should clinicians monitor the success, or lack of success, of brensocatib therapy, once a patient has been committed to this treatment? How do you know, based on symptoms and other metrics, that the drug is working in your patients with NCFBE? And what side effects, if any, should be anticipated?

QUESTION # 66: Does monitoring pulmonary function help clinicians monitor the drug effects or, possibly, improve patient compliance?

QUESTION # 67: How are brensocatib and other investigational drugs in the pipeline shaping/changing the multimodal treatment landscape for NCFBE? And how to educate patients in whom you are considering starting/using this novel therapy?