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Periodontal Effects of the Reversible Dipeptidyl Peptidase 1 Inhibitor Brensocatib in Bronchiectasis

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Abstract: ***Aims:*** *Brensocatib is a reversible inhibitor of dipeptidyl peptidase 1 (cathepsin C), in development to treat chronic non–cystic fibrosis bronchiectasis. The phase 2, randomized, placebo-controlled WILLOW trial (NCT03218917) was conducted to examine whether brensocatib reduced the incidence of pulmonary exacerbations. Brensocatib prolonged the time to the first exacerbation and led to fewer exacerbations than placebo. Because brensocatib potentially affects oral tissues due to its action on neutrophil-mediated inflammation, we analyzed periodontal outcomes in the trial participants.*

Materials and Methods: *Patients with bronchiectasis were randomized 1:1:1 to receive once-daily oral brensocatib 10 or 25 mg or placebo. Periodontal status was monitored throughout the 24-week trial in a prespecified safety analysis. Periodontal pocket depth (PPD) at screening, week 8, and week 24 was evaluated. Gingival inflammation was evaluated by a combination of assessing bleeding upon probing and monitoring the Löe-Silness Gingival Index on 3 facial surfaces and the mid-lingual surface.*

Results: *At week 24, mean ± SE PPD reductions were similar across treatment groups: −0.07 ± 0.007, −0.06 ± 0.007, and −0.15 ± 0.007 mm with brensocatib 10 mg, brensocatib 25 mg, and placebo, respectively. The distribution of changes in PPD and the number of patients with multiple increased PPD sites were similar across treatment groups at weeks 8 and 24. The frequencies of gingival index values were generally similar across treatment groups at each assessment. An increase in index values 0–1 and a decrease in index values 2–3 over time and at the end of the study were observed in all groups, indicating improved oral health.*

Conclusions: *In patients with non–cystic fibrosis bronchiectasis, brensocatib 10 or 25 mg had an acceptable safety profile after 6 months' treatment, with no changes in periodontal status noted. Improvement in oral health at end of the study may be due to regular dental care during the trial and independent of brensocatib treatment.*

Knowledge Transfer Statement: *The results of this study suggest that 24 weeks of treatment with brensocatib does not affect periodontal disease progression. This information can be used by clinicians when considering treatment approaches for bronchiectasis and suggests that the use of brensocatib will not be limited by periodontal disease risks. Nevertheless, routine dental/periodontal care should be provided to patients irrespective of brensocatib treatment.*

Keywords: clinical trial, immunology, pathogenesis, inflammation mediators, neutrophils, elastase

Introduction

Neutrophil serine proteases (NSPs), including neutrophil elastase, cathepsin G, and proteinase 3, are proteolytic enzymes that regulate inflammatory processes and contribute to the

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nonoxidative destruction of intracellular and extracellular pathogens (Pham 2006; Korkmaz et al. 2010; Majewski et al. 2016). Activated NSPs are packaged in cytoplasmic granules within neutrophils, the leukocytes that form the first line of defense against invading microbes, including those of the oral microbiome (Korkmaz et al. 2010). Neutrophil dysregulation and hyperresponsiveness, as well as excessive secretion of active NSPs, have been implicated in the common inflammatory condition periodontitis, as well as in numerous inflammatory respiratory diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, and bronchiectasis (Korkmaz et al. 2010; Hajishengallis et al. 2015; Gramegna et al. 2017). Therefore, treatments that target neutrophils, neutrophil recruitment, or NSPs have the potential to affect the periodontal ligament and other connective tissues.

Dipeptidyl peptidase 1 (DPP-1; also known as cathepsin C) is an enzyme responsible for activation of NSPs during neutrophil maturation in the bone marrow (Palmér et al. 2018). Activation of neutrophils leads to the release of NSPs as well as the formation of neutrophil extracellular traps (NETs) containing neutrophil elastase and antimicrobial factors such as myeloperoxidase (Papayannopoulos et al. 2010). NETs play a role in immune defense, but excessive NET formation can be cytotoxic (Twaddell et al. 2019). Increased activity of neutrophil elastase and other NSPs can overwhelm natural inhibitors, leading to an increased risk of infection (Vandivier et al. 2002; Dubois et al. 2012; Chalmers and Hill 2013; Sibila et al. 2019). Thus, targeting the activity of DPP-1 is an attractive therapeutic strategy for inflammatory diseases involving NSPs. However, therapies aimed at altering DPP-1 function must consider potential oral cavity–related adverse events associated with perturbations in neutrophil function. For example, Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive condition in which a near-total reduction in DPP-1 activity results in severe prepubertal periodontitis and premature loss of deciduous and permanent teeth (Firatli et al. 1996; Pham et al. 2004; Papayannopoulos et al. 2010; Roberts et al. 2016; Shawli et al. 2020). The inability to eliminate periodontal pathogens as a result of DPP-1 deficiency is thought to underlie the mechanism of periodontitis in PLS; however, patients with PLS also have numerous functional defects in neutrophil activity, such as impaired chemotaxis, an inability to generate NETs, release of higher-than-normal levels of proinflammatory cytokines, and formation of elevated reactive oxygen species (Roberts et al. 2016). Yet patients with PLS do not typically experience chronic systemic infections; rather, the observed neutrophil defects appear to be localized to anatomical areas subjected to robust chronic microbial challenge. In the mouth, the neutrophil response to this microbial challenge results in a cycle of gingival inflammation and destruction that can lead to periodontitis and premature tooth loss (Roberts et al. 2016).

Brensocatib is a small-molecule, orally bioavailable, selective, competitive, and reversible inhibitor of DPP-1 under investigation for the treatment of patients with the chronic lung disease non–cystic fibrosis bronchiectasis. In the phase 2 WILLOW trial (ClinicalTrials.gov identifier NCT03218917; EudraCT number: 2017-002533-32), patients with non–cystic fibrosis bronchiectasis received once-daily oral brensocatib 10 or 25 mg or placebo for 24 weeks (Chalmers et al. 2020). Treatment with brensocatib in patients with bronchiectasis was associated with reduced neutrophil elastase activity in sputum from baseline over the 24-week treatment period and improvements in bronchiectasis clinical outcomes, prolonging the time to first exacerbation compared with placebo (Chalmers et al. 2020).

Because of the theoretical risk that treatment with brensocatib and reduction in DPP-1 may result in the initiation or progression of periodontal disease, dental outcomes were a key focus in the WILLOW trial. Although we did not measure DPP-1 activity during the WILLOW trial, it is not expected to reach the same reduction as seen in PLS. Chalmers et al. (2020) found that the incidence of dental adverse events of special interest was higher in the 10-mg brensocatib dose group than in the placebo group. However, across the trial groups, the numbers of patients with dental sites that had an increase of at least 2 mm in the pocket depth and an absolute depth of at least 5 mm (the threshold of concern in periodontal disease) were evenly distributed, which suggests that there was no difference in the progression of periodontal disease between treatment groups (Chalmers et al. 2020). We performed this analysis to provide a more detailed description of the periodontal findings from the WILLOW trial. This report describes results from dental monitoring of the WILLOW trial, which contributes additional information on the role of neutrophils in periodontal pathogenesis. The objective of this study was to determine the effects of brensocatib treatment on periodontal outcomes by measuring periodontal pocket depth and gingival inflammation during treatment.

Materials and Methods

Trial Design and Patient Eligibility

The phase 2, double-blind, parallel-group WILLOW trial was conducted at 116 clinical sites in 14 countries in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association 2013) and the Good Clinical Practice guidelines of the International Council for Harmonisation (International Conference on Harmonisation 2001). The complete materials and methods have been previously reported in the primary publication (Chalmers et al. 2020). As described in the primary publication, this study complied with CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines, and all participants provided written informed consent. Briefly, eligible adults (aged 18 to 85 y) with confirmed bronchiectasis

and at least 2 exacerbations in the previous 12 mo were randomized 1:1:1 to receive once-daily oral brensocatib 10 mg, brensocatib 25 mg, or placebo for 24 weeks. Because of the possibility of oral side effects as a result of the mechanism of action of brensocatib, patients with severe periodontitis, defined as pocket depths and attachment losses of ≥6 mm on 2 or more teeth, were excluded from trial participation, as were those scheduled to have tooth extraction during the trial period. Patients were excluded if any teeth had class 3 mobility or furcation involvement or any potential infections from oral conditions such as dental caries, endodontic infections, or oral lesions that were not corrected before the trial. Patients with PLS were also excluded from the trial.

The primary efficacy end point was the time to first exacerbation of bronchiectasis symptoms. Safety end points included treatment-emergent adverse events, clinical laboratory assessments, vital signs, and physical examination results, including examination of the oral soft tissue and skin. Results for the primary and secondary efficacy end points and safety measures were reported in the primary publication (Chalmers et al. 2020). This analysis of the oral data was performed to determine the effect of brensocatib 10 or 25 mg on the periodontal and gingival health of trial participants over 24 weeks of treatment. A secondary goal was to ensure that treatment with brensocatib did not exacerbate gingival inflammation or result in increased periodontal pocket increases consistent with periodontal progression over the 24-week treatment phase.

Oral Examinations

All dentate patients underwent oral assessment at baseline and weeks 8 and 24. The initial oral examination consisted of inspection of hard and soft tissues, a full periodontal assessment, bitewing radiographs, and either a complete full-mouth series of radiographs or a panoramic radiograph. Participants who had had full-mouth dental radiographs taken within 6 mo of baseline that were available for review were not required to have another set of dental radiographs taken at the first study visit. The initial examination was designed to provide baseline information on the periodontal condition of patients and to screen for patients with oral infections or severe periodontal disease.

Dental Evaluations

Eligible patients received oral hygiene instruction, and depending on the subject's periodontal health, supra- and subgingival scaling and root planing was provided during the screening period prior to randomization. Any sites with a >2-mm change in periodontal pocket depth (PPD) were root planed and scaled. Oral and dental inspection was performed by the investigator at each subsequent study visit; upon discovery of any signs or symptoms of oral infection, gingivitis, periodontitis, or progression of the preexisting conditions, the patient was referred to the study-designated dentist for further assessment. Oral examinations were conducted by a dentist or periodontist at screening and repeated at 8 and 24 weeks to monitor the stability of the gingival and periodontal status. Patients with signs of progressing periodontal disease over the course of the trial were to be discontinued from trial medication but were maintained in the trial until the 24-week examination.

Due to the large number of clinical sites (116) across 14 countries, dental examiners could not be calibrated, nor could a meaningful center effect be estimated as the sample size was very small for each center. Clinical attachment levels (CALs), cemento-enamel junction (CEJ), and PPD measurements were taken at 6 sites per tooth. However, CEJ measurements across centers were inconsistent, and as was clear during the enrollment results and early results at the week 8 clinical visit, CAL measurements were not consistent enough to monitor progression of periodontal disease. Therefore, PPD was used to monitor periodontal disease progression.

Periodontal measurements were performed with a North Carolina Periodontal Probe. If measurements fell between the 1-mm markings, the lower value was recorded. Six periodontal sites were measured per tooth in up to 32 teeth per patient at each evaluation. At the 8-week and 24-week visits, any periodontal site with an additional ≥2 mm in pocket depth compared with the prior visit was remeasured to verify the measurements, and the site was root planed and scaled. The study periodontist reviewed the record of any subject at the 8-week visit who had more than 2 teeth with an increase of pocket depth of ≥2 mm and/or a change in pocket depth of >6 mm at 1 or more sites. The study periodontist, who was blinded to group assignment, used these determinants to assess whether the changes in pocket depth were consistent with periodontal progression (i.e., more than 2 sites with ≥2 mm increased pocket depth or an isolated site with more severe progression) or occurred due to measurement error. If the measurement was determined to be consistent with periodontal progression, the patient was to be discontinued from the trial medication but was maintained in the trial until the 24-week examination.

Gingival inflammation was evaluated by a combination of the assessment of bleeding upon probing (yes or no) and the Löe–Silness Gingival Index (Loe 1967) on 3 facial surfaces (mesial, facial, distal) and the mid-lingual surface (4/tooth). The gingival index is scored 0, 1, 2, or 3, with a score of 0 indicating healthy gingiva, 1 indicating mild inflammation with no bleeding on probing, 2 indicating moderate inflammation with bleeding on probing, and 3 indicating severe inflammation with spontaneous bleeding (Loe 1967). In the trial, we simplified the evaluation of the gingival health as follows: the values of 0–1 were used if no bleeding occurred when a probe was swept in the sulcus, and values of 2–3 were used if the sulcus was bleeding and/or markedly inflamed, resulting in the reporting of either 0–1 or 2–3.

Dental-related safety events were reported throughout the 24-week treatment

Table 1.
Baseline Demographics of Dentate Patients.

Characteristic	Placebo ($n = 78$)	Brensocatib 10 mg ($n = 76$)	Brensocatib 25 mg ($n = 75$)
Age, mean (SE), y	62.9 (1.4)	64.4 (1.5)	62.8 (1.5)
Female, *n* (%)	49 (62.8)	54 (71.1)	52 (69.3)
Race, *n* (%)			
White	64 (82.1)	71 (93.4)	67 (89.3)
Asian	12 (15.4)	4 (5.3)	5 (6.7)
Black	2 (2.6)	0	2 (2.7)
Other[a]	0 (0)	1 (1.3)	1 (1.3)
Baseline PPD	($n = 77$)	($n = 75$)	($n = 77$)
Mean ± SE (95% CI)	2.13 ± 0.009 (2.11–2.15)	2.10 ± 0.01 (2.08–2.12)	2.09 ± 0.009 (2.08–2.11)
Baseline GI index score	($n = 73$)	($n = 73$)	($n = 76$)
Frequency, %			
0–1	85.2	85.6	87.9
2–3	14.8	14.4	12.1

CI, confidence interval; GI, gingival inflammation; PPD, periodontal pocket depth; SE, standard error.
[a]Includes Native American, Alaskan Native, Native Hawaiian, and Other Pacific Islander.

phase and the 4-week follow-up period. A data monitoring committee included a periodontal expert (F.A. Scannapieco), who evaluated the requested dental safety information provided by the trial team.

Statistical Analyses

Since periodontal measures were part of the safety assessment, the trial was not powered to examine statistical differences in periodontal measures between treatment groups; therefore, the analyses are descriptive only. The distributions of mean changes in PPD for each treatment group were compared to determine the frequencies and direction of changes over 8 and 24 weeks. Last, the frequency of gingival inflammation was compared by summarizing the distribution of inflamed sites at baseline and weeks 8 and 24.

Results

Patients

Of 256 patients randomized to receive treatment, 229 (89.5%) were dentate and received either brensocatib 10 mg ($n = 76$), brensocatib 25 mg ($n = 75$), or placebo ($n = 78$). Demographic and clinical characteristics were similar across treatment groups. Patients were predominantly female and White with a mean age ranging from 63 to 64 years (Table 1). Mean PPD values at baseline were approximately 2 mm in each treatment group (Tables 1 and 2). None of the patients discontinued the study due to dental-related adverse events or periodontal progression (including patients who were referred to the dental consultant for an increase in pocket depth of ≥2 mm and/or a change in pocket depth of >6 mm at week 8). In 1 patient, brensocatib was discontinued at week 24 (end of treatment) due to several areas of periodontal progression, with a pocket depth of >6 mm in more than 2 teeth.

Changes in PPD

Pocket depth was examined in the same way in all patients, and no difference in the frequency of change in PPD between brensocatib or placebo groups was found, with similar distributions of changes in PPD at week 8 (Fig. 1A) and week 24 (Fig. 1B). Furthermore, PPD changes from baseline showed small reductions in PPD at both weeks 8 and 24 in all groups (a larger number of patients had decreased PPD from baseline [–1 to –4 mm] than increased PPD from baseline [1 to 9 mm]; Table 2). PPD changes were weighted toward a reduction in PPD (Fig. 1, Table 2), indicating that small improvements in the periodontal condition of all trial patients were found, regardless of treatment received (Fig. 1, Table 2).

PPD Increases

A similar number of patients in each treatment group experienced changes in PPD over 8 and 24 weeks of treatment. At week 8, a total of 29 patients (12.7%) experienced ≥3 changes in PPD of ≥2 mm: 10 patients in the brensocatib 10-mg group experienced a total of 84 increases in PPD (range, 3–32 per patient), and 10 patients in the brensocatib 25-mg

Table 2.
Baseline PPD and GI and Changes in PPD and GI at Weeks 8 and 24.[a]

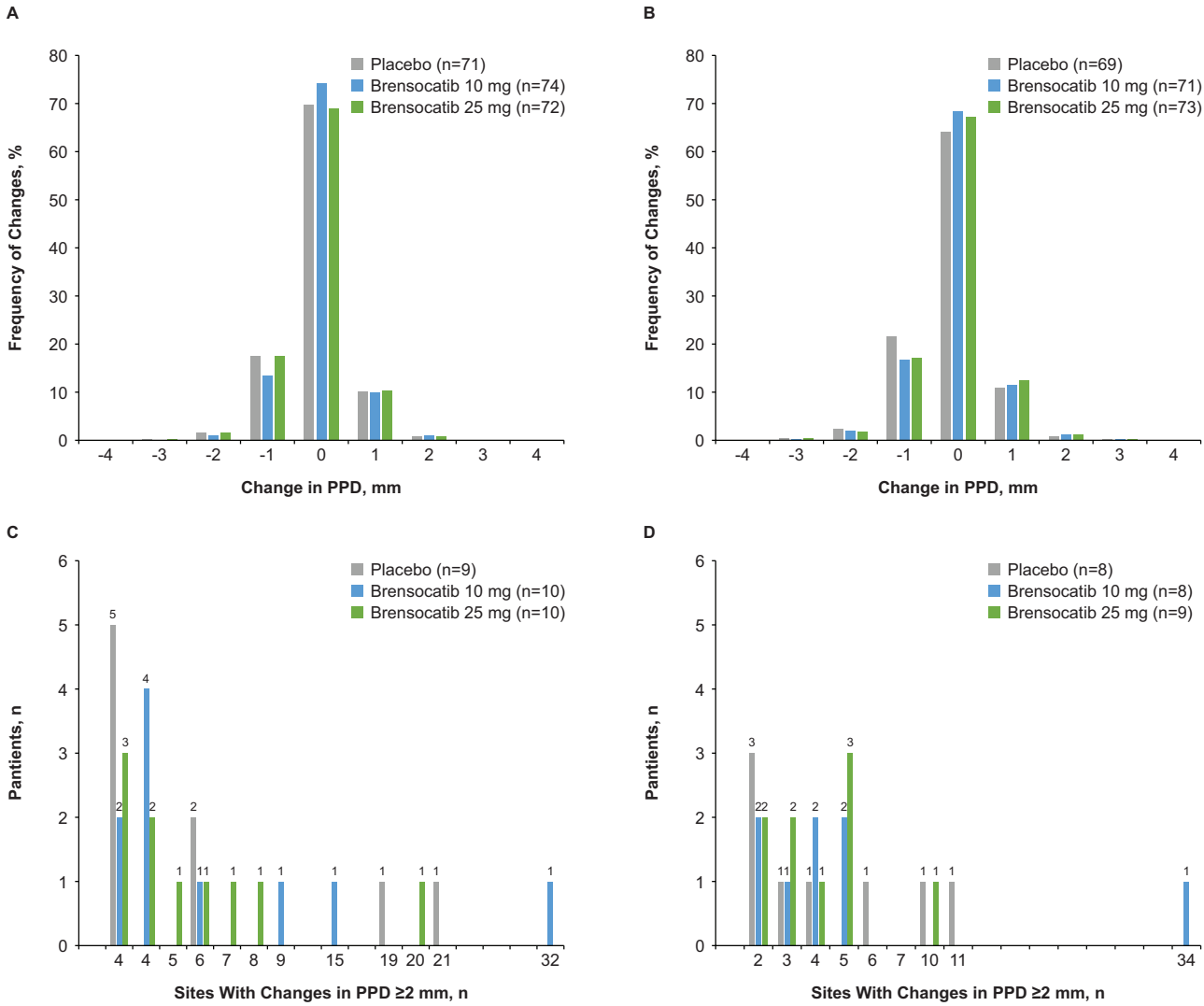
Characteristic	Placebo	Brensocatib 10 mg	Brensocatib 25 mg
Baseline PPD	*n* = 77	*n* = 75	*n* = 77
Mean ± SE (95% CI)	2.13 ± 0.009 (2.11 to 2.15)	2.10 ± 0.01 (2.08 to 2.12)	2.09 ± 0.009 (2.08 to 2.11)
Change in PPD,[a] mean ± SE (95% CI)			
Week 8	*n* = 71	*n* = 74	*n* = 72
	–0.09 ± 0.006 (–0.10 to –0.08)	–0.03 ± 0.006 (–0.04 to –0.02)	–0.09 ± 0.006 (–0.10 to –0.07)
Week 24	*n* = 69	*n* = 71	*n* = 73
	–0.15 ± 0.007 (–0.16 to –0.13)	–0.07 ± 0.007 (–0.08 to –0.05)	–0.06 ± 0.007 (–0.07 to –0.05)

	No. of Pockets					
Level of PPD Changes, mm	Week 8 (*n* = 71)	Week 24 (*n* = 69)	Week 8 (*n* = 74)	Week 24 (*n* = 71)	Week 8 (*n* = 72)	Week 24 (*n* = 73)
–4	1	4	1	2	0	2
–3	15	32	4	17	16	27
–2	155	217	98	173	170	180
–1	1,706	2,029	1,300	1,555	1,722	1,719
0	6,806	6,055	7,172	6,316	6,735	6,810
1	983	1,024	970	1,058	1,023	1,265
2	76	65	97	98	86	112
3	5	7	9	18	5	11
4	3	0	0	1	1	2
5	0	0	1	0	0	0
9	0	0	1	0	1	0
Decreased PPD from BL (–1 to –4 mm)	1,877	2,282	1,403	1,747	1,908	1,928
Increased PPD from BL (1 to 9 mm)	1,067	1,096	1,078	1,175	1,116	1,390
No change in PPD	6,806	7,172	7,172	6,316	6,735	6,810

GI Index Score (Frequency, %)	Placebo	Brensocatib 10 mg	Brensocatib 25 mg
Baseline 0–1 2–3	*n* = 73 85.2 14.8	*n* = 73 85.6 14.4	*n* = 76 87.9 12.1
Week 8 0–1 2–3	*n* = 67 89.1 10.9	*n* = 69 88.6 11.4	*n* = 69 91.3 91.3
Week 24 0–1 2–3	*n* = 66 90.3 9.7	*n* = 67 92.6 7.4	*n* = 71 91.7 8.3

[a]A negative change indicates improvement in periodontitis.
BL, baseline; CI, confidence interval; GI, gingival inflammation; PPD, periodontal pocket depth; SE, standard error.

Figure 1. Changes in PPD at Weeks 8 and 24. (**A**) Distribution of Changes at Week 8. (**B**) Distribution of Changes at Week 24. (**C**) Patients with ≥3 Increases of ≥2 mm at Week 8. (**D**) Patients with ≥3 Increases of ≥2 mm at Week 24. PPD, periodontal pocket depth.

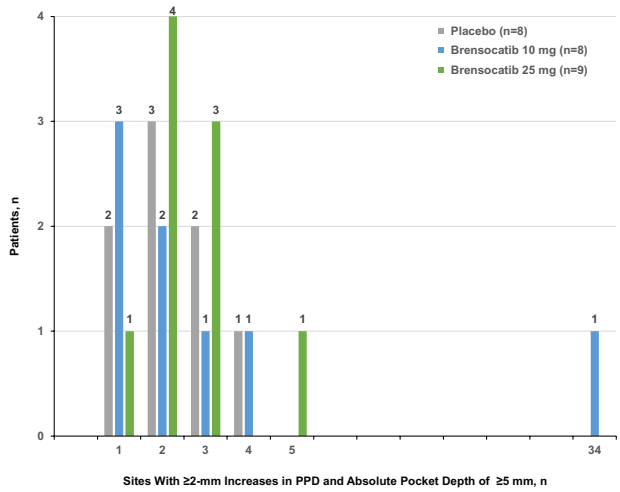


group experienced a total of 63 increases (range, 3–20 per patient) compared with 9 patients in the placebo group who experienced 67 increases (range, 3–21 per patient) (Fig. 1C); the median number of increases in PPD of ≥2 mm was 4 with 10 mg brensocatib, 4.5 with 25 mg brensocatib, and 3 with placebo. At week 24, a total of 25 patients (10.9%) experienced ≥3 sites with an increase of ≥2 mm in PPD: 8 patients in the brensocatib 10-mg group experienced a total of 59 increases (range, 2–34 per patient), and 9 patients in the brensocatib 25-mg group experienced a total of 39 increases (range, 2–10 per patient) compared with 8 patients in the placebo group who experienced 40 increases (range, 2–11 per patient) (Fig. 1D); the median number of sites was 4, 4, and 3.5, respectively. In these same patients, the median number of sites with an increase of ≥2 mm and an absolute pocket depth of ≥5 mm at week 24 was 2 in each treatment group (Fig. 2). One patient in the brensocatib 10-mg group had 34 sites with an increase of ≥2 mm and an absolute pocket depth of ≥5 mm.

Gingival Inflammation

The frequency of Löe–Silness Gingival Index values of 0–1 (healthy gums to mild inflammation) and 2–3 (moderate to severe inflammation) was generally similar across treatment groups at each assessment (baseline, weeks 8 and 24). The frequency of index values 0–1 increased slightly over time in each treatment group, from 85.2% at baseline to 89.1% and 90.3% at weeks 8 and 24 in the placebo group, from 85.6% at baseline to 88.6% and 92.6% at weeks 8 and 24 in the brensocatib 10-mg group, and from 87.9% at baseline to 91.3% and 91.7% at weeks 8 and 24 in the brensocatib 25-mg group (Table 2, Fig. 3). A corresponding decrease in index values 2–3 over time was observed, from

Figure 2. Patients with Increases of ≥2 mm and Absolute Pocket Depth of ≥5 mm (Week 24). PPD, periodontal pocket depth.



14.8% at baseline to 10.9% and 9.7% at weeks 8 and 24 in the placebo group, from 14.4% at baseline to 11.4% and 7.4% at weeks 8 and 24 in the brensocatib 10-mg group, and from 12.1% at baseline to 8.7% and 8.3% at weeks 8 and 24 in brensocatib 25-mg group (Table 2, Fig. 3). In all 3 groups, there was slight decrease in the percentage of Löe–Silness Gingival Index values of 2–3 at week 24, which may be reflective of initial periodontal therapy (scaling and root planing) and subsequent oral examinations during the study.

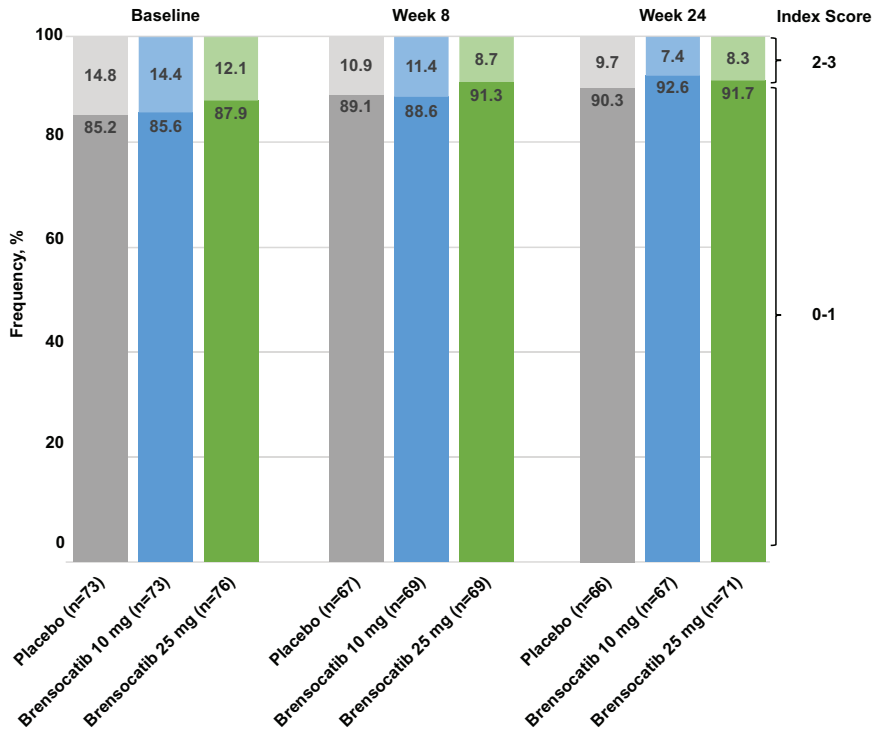
Discussion

Use of numerous types of drugs, including anti-inflammatory steroids, nonsteroidal anti-inflammatory drugs, immunosuppressants, and antihypertensives, is known to potentially cause changes in the pathways that can lead to periodontal disease (Heasman and Hughes 2014). Periodontal disease and poor oral health in general have been linked to numerous chronic and systemic conditions, including those of the respiratory tract, such as COPD, aspiration pneumonia, and pulmonary infection (Mojon 2002; Gomes-Filho et al. 2020; Scannapieco 2021). Concern over potential effects of the investigational DPP-1 inhibitor brensocatib on periodontal health was based on the manifestations of the rare genetic condition PLS, in which aggressive periodontitis leads to premature loss of deciduous and permanent dentition at a young age (Sørensen et al. 2014). Brensocatib is not expected to re-create the features of PLS as it is a reversible inhibitor that does not completely inhibit DPP-1 at the doses used in the WILLOW trial. Identifying the optimal balance between immune modulation and potential adverse effects is key in the development of new therapies, and this analysis adds further detail to the positive risk–benefit balance demonstrated in the phase 2 study by providing a more detailed description of the periodontal findings from the WILLOW trial (Chalmers et al. 2020).

The overall results for changes in PPD suggest improvement in periodontal health among all patients over the 24-week treatment phase of the study, which is likely due to all dentate patients receiving scaling and root planing at baseline along with the required dental examinations and evaluations at weeks 8 and 24. The distribution of PPD changes and the number of patients with greater periodontal progression were nearly identical for the brensocatib and placebo groups, and the percentage of patients with ≥3 sites of ≥2-mm increases in PPD and an absolute pocket depth of ≥5 mm, which is classified as stage III periodontal disease (Papapanou et al. 2018), was similar among active treatment and placebo, suggesting that brensocatib did not affect periodontal progression. Furthermore, gingival inflammation improved over the course of the study, indicating that DPP-1 inhibition from treatment with brensocatib likely does not affect the gingiva and that the regular treatments that all dentate patients received while participating in the trial improved their overall oral health. While the mechanism by which brensocatib may influence the observed effects on periodontal disease activity and gingival inflammation cannot be determined from the 24-week trial, DPP-1 inhibition by brensocatib likely reduces neutrophil-driven inflammation by preventing connective tissue destruction by NSPs. Further studies to determine the cellular effects of partial DPP-1 inhibition in periodontal tissues are required to understand how DPP-1 inhibition may affect other chronic inflammatory diseases such as periodontitis.

The periodontal results presented here have some limitations. First, periodontal disease is a slow process, and the detection of periodontal progression is difficult (Best et al. 1990). Since the treatment phase was only 24 weeks, the long-term effects of brensocatib on periodontal health remain unknown. Long-term safety studies are needed to confirm the effects of brensocatib on periodontal health. Second, CAL, which directly measures changes in periodontal disease and is normally used to monitor periodontal disease over time in clinical trials, consists of 2 measures: PPD and the location of the CEJ, although the difficulty in locating the CEJ tends to lead to greater error (Haffajee and Socransky 1986; Harris 2003; Offenbacher et al. 2009). Thus, PPD was used for monitoring the patients in this report. Third, although calibration exercises generally result in examiners agreeing in measurement to within 1 mm approximately 85% of the

Figure 3. Distribution of Gingival Inflammation (GI) by Index Score (0–1 or 2–3) at Baseline and Weeks 8 and 24. Higher index scores represent more inflammation.



time (Best et al. 1990), calibration of examiners in this study was not possible due to the large number of study sites across 14 countries. In addition, since this study was descriptive in nature and not hypothesis driven, no statistical analyses were conducted. Last, patients included in the trial did not have severe periodontal disease; those who had no, slight, or moderate periodontal disease underwent initial periodontal therapy and were closely monitored over the course of the trial, which is not reflective of typical dental health practices outside of a clinical trial setting. Routine dental care, periodontal treatment, and dental monitoring (every 3–6 months) should be provided to patients who will receive the treatment with brensocatib.

Conclusion

Brensocatib did not negatively affect periodontal health among patients with non–cystic fibrosis bronchiectasis who participated in the phase 2 WILLOW study. This study did not find significant increases in pocket depth or gingival health over 24 weeks of drug treatment. Oral health will continue to be monitored throughout the brensocatib clinical development program, in which the risk for periodontal disease over a longer treatment period will be evaluated. The evidence in this trial suggests that uncalibrated dentists and periodontists from multiple countries were not able to monitor periodontal changes by clinical attachment level but were able to monitor changes in pocket depth with a periodontal probe with 1-mm increments.

Authors' Contributions

J.C. Gunsolley, J.D. Chalmers, C. Fernandez, participated in research design; J.C. Gunsolley, developed the dental portion of the protocol, monitored periodontal/dental concerns during the trial, and suggested protocol changes as needed; F.A. Scannapieco, included on the Data Monitoring Committee; J.D. Chalmers, O. Sibila, trial investigators; J.C. Gunsolley, C. Fernandez, performed data analyses; all authors contributed to the writing of the manuscript.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: J.C. Gunsolley was a paid consultant (biostatistical and periodontal) for the WILLOW trial but received no compensation for the work on this manuscript. C. Fernandez is an employee of Insmed Incorporated. O. Sibila has received a grant from Zambon and personal or other fees from Bayer Healthcare, Insmed Incorporated, and Grifols. J.D. Chalmers has received grants and personal fees from AstraZeneca, Boehringer–Ingelheim, GSK, Zambon, and Insmed Incorporated; a grant from

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