BAUSCH Health

New Clinical Study Suggests the Use of OraPharma's ARESTIN® (minocycline HCl) Microspheres, 1mg May Decrease Certain Pathogens in Adults with Periodontitis

May 18, 2023

Novel Trial to Study the Reduction of Certain Pathogens Following Scaling and Root Planing Procedure

LAVAL, Quebec, May 18, 2023 – Bausch Health Companies Inc. (NYSE/TSX: BHC) and its oral health care business, OraPharma, today announced the publication of a new study, which showed that ARESTIN® (minocycline HCI) microspheres, 1mg decreased certain pathogenic burdens, also known as infection burdens, in adults with periodontitis when applied immediately after scaling and root planning (SRP) and again at a three-month reapplication, versus SRP alone. ARESTIN is an FDA-approved antibiotic applied locally to gum pockets in adults with periodontitis following an SRP procedure and is used as part of an overall oral health program. ARESTIN should not be used in people who are allergic to minocycline or tetracyclines.

The investigator-initiated trial, sponsored in part by Bausch Health, and conducted by researchers from the University of Minnesota School of Dentistry, appeared today in the *Journal of Periodontology.* The study showed minocycline application immediately after initial SRP and reapplication at 3-months after SRP decreased certain key pathogens and may have contributed to improvements in probing depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP) and gingival index (GI) compared to SRP alone.

"Dental practices need to think about periodontal disease and the role of keystone pathogens that originate in the mouth, can travel, and may be associated with other systemic outcomes such as diabetes and cardiovascular disease," said Richard Nagelberg, DDS, Director of Medical Affairs at Bausch Health. "This study represents an important path forward in helping to manage periodontal disease and we hope it encourages further research in the area of periodontal disease progression and how it may relate to the oral-systemic connection."

Since the pivotal trial, there was a gap in the literature on whether minocycline HCI microspheres, 1mg reduced specific periodontal pathogens. This study identified that the administration of minocycline HCI microspheres, 1mg did significantly decrease specific periodontal pathogens.

The objective of the study entitled, *Effect of Scaling and Root Planing With and Without Minocycline HCl Microspheres on Periodontal Pathogens and Clinical Outcomes: A Randomized Clinical Trial,* was to determine if minocycline HCl plus SRP contributed to the improvement of certain clinical measures commonly seen in patients with gum disease. A secondary endpoint was to determine if minocycline microspheres HCl with SRP lowered specific pathogens responsible for periodontitis compared to SRP alone. Saliva and clinical outcomes were collected for both groups at baseline before SRP, 1-month reevaluation, and at 3 and 6-month periodontal recall. Minocycline microspheres (MM) were delivered to pockets ≥5 mm immediately after SRP and immediately after the 3-month periodontal maintenance. This study reported that of the 11

pathogens that play an instrumental role in periodontitis, there were six periodontal pathogens that had a statistically significant decrease at 1-month and four periodontal pathogens with a statistically significant decrease at the 6-month periodontal maintenance versus the SRP group alone. This study also reported that minocycline HCI plus SRP achieved greater improvement for probing depth, bleeding on probing, gingival index, and improvement in clinical attachment loss by the six-month periodontal maintenance versus SRP alone.

Limitations of the study include the lack of a blinded examiner for clinical outcomes and lack of patient-reported outcome measures. The principal investigator (PI) collected saliva, recorded clinical measures and provided treatment for both groups. The participants in this study were predominantly from the Midwestern region, Caucasian and over the age of 50 years old, which does not represent the general population of individuals with periodontitis.

"There was a larger decrease of Tannerella forsythia, Treponema denticola, Fusobacterium nucleatum/periodonticum, Prevotella intermedia, Parvimonas micra and Eikenella corrodens in the SRP + MM group," said Dr. Nagelberg. It is notable that minocycline HCl microspheres, 1mg immediately following SRP procedures reduced these specific periodontal pathogens by the 1-month reevaluation.

The previous pivotal study (Williams et al., 2001) was conducted to determine if minocycline HCI plus SRP reduced pocket depth in patients with generalized moderate to advanced adult periodontitis versus SRP alone. Subjects treated with minocycline HCI plus SRP were found to have statistically significantly reduced probing pocket depth compared with those treated with SRP alone or SRP + vehicle at 9 months after initial treatment.

About the Study

A total of 70 participants were randomized to receive SRP alone, or SRP with minocycline HCl microspheres, 1mg following the procedure, and again at the 3-month periodontal visit. Participants in both groups received periodontal evaluations at baseline, one month, three months and six months following the initial SRP procedure. The primary goal of this study was to determine the adjunctive effects of minocycline microspheres (MM) on clinical outcomes of PD, CAL, BOP, and GI after SRP+MM compared to SRP alone. Secondary outcome variables were the relative numbers of 11 periodontal pathogens in saliva after SRP+MM compared to SRP alone. The bacterial load and pathogenic burden were determined using a salivary test.

Microorganisms and secondary periodontal measurements were compared between groups using generalized linear mixed-effects models, with fixed effects for group, visit, site (for clinical measurements), and group-by-visit and group-by-site interactions, and random effects for participant and site within participant. Mean changes from baseline were compared between groups via group-by-visit interaction tests.

The six periodontal pathogens observed in the test group to have a statistically significant decrease compared to the SRP alone group at the one-month follow-up visit were *Tannerella forsythia (Tf)* (0.003), *Treponema denticola(Td)* (0.01), *Fusobacterium nucleatum/periodonticum (Fn/Fp)(*0.0009*), Prevotella intermedia (Pi)* (0.04), *Parvimonas micra (Pm)* (<0.0001), *andEikenella corrodens (Ec)* (0.02). Further, the four periodontal pathogens observed in the test group to have a statistically significant decrease compared to the SRP alone group at the final six-month visit were *Fusobacterium nucleatum/periodonticum (Fn/Fp)* (0.02), *Prevotella intermedia* (0.05), *Campylobacter rectus (Cr)* (0.04) and *Eikenella corrodens* (0.0002).

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predominantly from the Midwestern region, Caucasian and over the age of 50 years old, which does not represent the general population of individuals with periodontitis.

The statistical analysis for this research was supported by a grant from the National Institutes of Health's National Center for Advancing Translational Science.

Important Safety Information for ARESTIN®

INDICATION

ARESTIN® (minocycline HCl) Microspheres, 1mg is indicated as an adjunct to scaling and root planing (SRP) procedures for reduction of pocket depth in patients with adult periodontitis. ARESTIN may be used as part of a periodontal maintenance program, which includes good oral hygiene and SRP.

IMPORTANT SAFETY INFORMATION

ARESTIN is contraindicated in any patient who has a known sensitivity to minocycline or tetracyclines. Hypersensitivity reactions and hypersensitivity syndrome that included, but were not limited to anaphylaxis, anaphylactoid reaction, angioneurotic edema, urticaria, rash, eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis may be present. Swelling of the face, pruritus, fever and lymphadenopathy have been reported with the use of ARESTIN. Some of these reactions were serious. Post-marketing cases of anaphylaxis and serious skin reactions such as Stevens Johnson syndrome and erythema multiforme have been reported with oral minocycline, as well as acute photosensitivity reactions.

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH, AND THEREFORE SHOULD NOT BE USED IN CHILDREN OR IN PREGNANT OR NURSING WOMEN.

Tetracyclines, including oral minocycline, have been associated with development of autoimmune syndromes including a lupus-like syndrome manifested by arthralgia, myalgia, rash, and swelling. Sporadic cases of serum sickness-like reaction have presented shortly after oral minocycline use, manifested by fever, rash, arthralgia, lymphadenopathy and malaise. In symptomatic patients, diagnostic tests should be performed and ARESTIN treatment discontinued.

The use of ARESTIN in an acutely abscessed periodontal pocket or for use in the regeneration of alveolar bone has not been studied.

The safety and effectiveness of ARESTIN has not been established in immunocompromised patients or in those with coexistent oral candidiasis. Use with caution if there is a predisposition to oral candidiasis.

In clinical trials, the most frequently reported nondental treatment-emergent adverse events were headache, infection, flu syndrome, and pain.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch
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Click
here
for full Prescribing Information.

About ARESTIN

ARESTIN® is an FDA-approved antibiotic applied locally to gum pockets in adults with periodontitis following an SRP procedure and is used as part of an overall oral health program. ARESTIN should not be used in people who are allergic to minocycline or tetracyclines.

In 2001, a pivotal study was conducted to: 1) determine whether the administration of minocycline microspheres would enhance the therapeutic effect of scaling and root planing in patients with chronic periodontitis, and 2) determine whether the compound was safe and well tolerated.

Seven hundred forty-eight (748) patients with moderate to advanced periodontitis were enrolled in an investigator-blind, multi-center trial and randomized to 1 of 3 treatment arms: 1) scaling and root planing (SRP) alone; 2) SRP plus vehicle; or 3) SRP plus minocycline microspheres. The primary outcome measure was probing depth reduction at 9 months. Clinical assessments were performed at baseline and 1, 3, 6, and 9 months.

Minocycline microspheres plus scaling and root planing provided substantially more probing depth reduction than either SRP alone or SRP plus vehicle. The difference reached statistical significance after the first month and was maintained throughout the trial. The improved outcome was observed to be independent of patients' smoking status, age, gender, or baseline disease level. There was no difference in the incidence of adverse effects among treatment groups.

About Periodontitis Risks
According to the National Health and Nutrition Examination Survey (NHANES), 42.2% of United States adults have periodontitis. There are certain factors that increase the risk for developing gum disease which include smoking, diabetes, poor oral hygiene, obesity and diabetes. In addition, gum disease may provide a gateway for bacteria to enter the body and trigger systemic health issues and inflammation in the body, though further research is necessary.

About OraPharma

OraPharma is a specialty pharmaceutical company committed to partnering with dental professionals to improve oral health. Founded more than 25 years ago, OraPharma includes a curated portfolio of treatments for periodontal disease and multiple regenerative solutions for oral surgery. More information can be found at
https://www.orapharma.com/
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About Bausch Health

Bausch Health Companies Inc. (NYSE/TSX: BHC) is a global diversified pharmaceutical company whose mission is to improve people’s lives with our health care products. We develop, manufacture and market a range of products primarily in gastroenterology, hepatology, neurology, dermatology, international pharmaceuticals and eye health, through our controlling interest in Bausch + Lomb. With our leading durable brands, we are delivering on our commitments as we build an innovative company dedicated to advancing global health. For more information, visit
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