

# Locally Delivered Antimicrobials: Clinical Evidence and Relevance

David W. Paquette, DMD, MPH, DMSc; Maria Emanuel Ryan, DDS, PhD; Rebecca S. Wilder, RDH, BS, MS

## Introduction

Periodontal disease is a common, mixed oral infection affecting the supporting structures around the teeth. While 75% of the adult population has at least mild periodontal disease (gingivitis), 20%-30% exhibits the severe destructive form (chronic periodontitis).<sup>1</sup> Characteristically, the disease is silent until the advanced stage when patients may report symptoms like swelling (abscess), discomfort, shifting of the dentition, or tooth mobility. The clinical signs of periodontitis emanate from inflammatory and destructive changes in the gingiva, connective tissues, alveolar bone, periodontal ligament, and root cementum. These signs include the formation of periodontal pockets, loss of clinical attachment, and resorption of alveolar bone.<sup>2</sup>

Accordingly, periodontitis begins with a pathogenic shift in the bacterial flora around teeth. Gram-negative organisms, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola* and *Aggregatibacter* (formally *Actinobacillus*) actinomycetemcomitans, predominate in the subgingival space and organize as a biofilm.<sup>3</sup> Several of the gram-negative bacteria in the biofilm are particularly important because they have been identified as red-complex bacteria (*T. forsythia*, *P. gingivalis*, and *T. denticola*) and have been linked with important parameters of periodontal diagnosis, such as pocket depth and bleeding on probing.<sup>3</sup> This bacterial biofilm is in direct contact with host tissues along an ulcerated epithelial interface called a periodontal pocket. Locally, bacteria and their products (eg, lipopolysaccharide endotoxin) penetrate host periodontal tissues and stimulate host expression of inflammatory mediators like arachidonic acid metabolites (prostaglandin E2) and cytokines (interleukin-1).<sup>4</sup> These mediators in turn trigger local inflammatory and destructive changes in the tissues.

## Abstract

Periodontitis is a common oral infection and inflammatory condition. Following treatment, residual or persistent periodontal inflammation is associated with disease progression and tooth loss. Cumulative evidence from clinical trials and meta-analyses support a complementary medical-mechanical model that combines locally delivered antimicrobials with scaling and root planing for the treatment of chronic periodontitis. Accordingly, greater pocket depth reductions and/or attachment level gains occur in patients treated with adjunctive locally administered antimicrobials (eg, tetracycline, chlorhexidine, doxycycline, and minocycline). These responses are clinically relevant because they are accompanied by a higher probability of patient maintenance or pocket resolution. Recent trials also indicate that locally administered antimicrobials may enhance the effects of periodontal surgical therapy and may reduce the signs of peri-implantitis. The consistency of these findings supports the use of locally administered antimicrobials for managing dental patients with chronic periodontitis.

**Keywords:** periodontitis, antibiotics, antimicrobials, local delivery, peri-implantitis, scaling and root planing

Longitudinal population studies indicate that these destructive changes (disease progression) are not continuous over time but appear restricted to “random bursts” of activity confined to short intervals (6 months or less).<sup>5</sup> Risk factors associated with progressive periodontitis include smoking, diabetes, obesity, poor plaque control, and certain genetic polymorphisms.<sup>6-10</sup> In addition, residual or persistent deep probing depths are associated with periodontitis progression.<sup>11</sup> Paulander and coworkers recently demonstrated that periodontitis subjects with moderate (4-5 mm) and deep (> 6 mm) probing depths were 2 to 3 times more likely to exhibit alveolar bone loss over 10 years.<sup>12</sup> Similarly for tooth loss, the odds ratio for moderate pockets was 2.9 (95% CI, 1.9-4.2), and the odds for deep pockets was 4.2 (95% CI, 2.4-7.3). These data imply pocket depth reduction (or resolution) is a clinically important treatment goal to ensure stability and maintenance in patients.

## Complementary Medical-Mechanical Treatment Model with Adjunctive Antimicrobials

Strategies for treating periodontitis principally focus on addressing the etiologic bacteria or biofilm.<sup>13,14</sup> According to the mechanical model, the bacterial biofilm is disrupted and removed via scaling and root planing (SRP) procedures. These debridement procedures can be accomplished nonsurgically or surgically, and both approaches result in pocket depth (PD) reductions in patients.<sup>15,16</sup> In addition, a number of adjunctive chemotherapeutic approaches have been developed, tested and approved for use in patients with chronic periodontitis (Table 1). These “locally delivered antimicrobials” follow a complementary medical-mechanical treatment model since they are used in combination with SRP for enhanced efficacy. These formulations typically cou-

**Table 1.** Summary of FDA-approved locally administered antimicrobials and clinical evidence from pivotal trials.

Locally Administered Antimicrobial	Active Agent	Polymer	Pivotal Trial Reference	Number of Subjects	Experimental Treatment	Controls	Results
Periochip®	Chlorhexidine gluconate (2.5 mg)	Cross-linked hydrolyzed gelatin	25	447	Periochip® plus SRP (adjunct)	Placebo chip plus SRP SRP alone	Periochip® plus SRP significantly reduced PD and increased CAL at 9 months compared to SRP alone.
Atridox®	Doxycycline (10% or 50 mg)	poly DL-lactide	29	411	Atridox® alone (monotherapy)	Placebo gel, SRP alone, no treatment	Treatment with Atridox® alone produced improvements in PD and CAL at 9 months that were equivalent to SRP alone.
Arestin®	Minocycline (1 mg)	Polyglycolide-co-dl-lactide	33	748	Arestin® plus SRP (adjunct)	Placebo microspheres plus SRP, SRP alone	Subjects treated with Arestin® plus SRP exhibited significantly greater PD reductions at 1, 3, 6, and 9 months versus SRP alone.

ple an antimicrobial or antibiotic with a drug polymer that extends drug release within the periodontal pocket (controlled-release delivery).<sup>17</sup>

A recent systematic review and meta-analysis conducted by Hanes and coworkers demonstrated that adjunctive locally administered antimicrobials improved PD over SRP alone in chronic periodontitis patients.<sup>18</sup> This group of investigators searched electronic databases and relevant dental journals and identified 32 clinical studies fitting selection criteria. The studies (28 randomized controlled clinical trials, 2 cohort, and 2 case-control studies) represented a variety of locally administered antimicrobials (eg, minocycline, doxycycline, tetracycline, metronidazole, and chlorhexidine formulations). The resulting meta-analysis indicated an overall significant reduction in PD with adjunctive local antimicrobials versus SRP alone. These findings strongly support the use of locally administered antimicrobials in combination with SRP in patients with chronic periodontitis, especially those at risk for disease progression.

The first local delivery system approved for use by the US Food and Drug Administration (FDA) was called Actisite® (ALZA Corporation, Palo Alto, Calif, USA) and was developed by Dr. Max Goodson in 1983.<sup>19</sup> This product consisted of a nonresorbable polymer fiber of ethyl vinyl acetate containing tetracycline hydrochloride (25% or 12.7 mg). Each fiber (23 cm) was placed subgingivally similar to retraction cord. Since that time, clinicians have been

introduced to second generation locally delivered antimicrobials that are easier to utilize and produce greater clinically significant results. Following is a discussion about the 3 products currently available in the United States.

### Chlorhexidine Gluconate Chip

The PerioChip® (Dexcel Technologies Limited, Jerusalem, Israel) is a biodegradable gelatin-based polymer system containing the active antimicrobial, chlorhexidine gluconate (2.5 mg). Each chlorhexidine (CHX)-gelatin wafer or chip is placed subgingivally with cotton pliers. While pharmacokinetic studies indicate that chlorhexidine is released from the system for 7-10 days in periodontal pockets, microbial studies have shown suppression of the pocket flora for up to 11 weeks following CHX chip treatment.<sup>20,21</sup> In the phase 3 clinical trials, CHX chip treatment plus SRP significantly reduced PD and maintained CAL at 9 months compared with SRP controls.<sup>22</sup> Importantly, SRP was limited in these trials to one hour of ultrasonic scaling. In addition, retreatment with CHX chip occurred at 3 and 6 months at sites with residual pockets (> 5 mm). Nevertheless, after 9 months of adjunctive CHX chip treatment, no sites exhibited bone loss, and 25% of the sites exhibited bone gain as measured with subtraction radiography.<sup>23</sup> In contrast, 15% of periodontal sites treated with SRP alone exhibited bone loss.

Chlorhexidine gluconate chip has a documented safety profile, and unlike chlorhexidine mouthrinse, does not cause any visible staining of teeth.

### Doxycycline Bioresorbable Gel

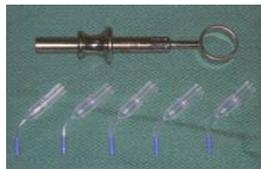
Atridox® (Atrix Laboratories, Fort Collins, Colo, USA) is a 10% formulation of doxycycline (50 mg) in a bioresorbable gel system (poly DL-lactide and N-methyl-2-pyrrolidone mixture). The system is supplied as 2 pre-filled syringes that are mixed chair-side and applied subgingivally to the base periodontal pockets using a syringe. The “flowable” polymer gel fills and conforms to pocket morphology, then solidifies to a wax-like consistency upon contact with gingival crevicular fluid. Doxycycline is released at effective concentrations over 7 days, and significant reductions (60%) in anaerobic pathogens are sustained for up to 6 months posttreatment.<sup>24,25</sup> In subjects with chronic periodontitis, the application of doxycycline gel (at baseline and 4 months later) reduced PD (1.3 mm) and improved CAL (0.8 mm) comparable to SRP alone at 9 months following treatment.<sup>26</sup> While current and former smokers within the trials did not respond as well to SRP alone, smoking status did not diminish the clinical improvements observed with doxycycline gel.<sup>27</sup> While these studies demonstrated equivalency of doxycycline gel (monotherapy) with SRP and supported regulatory approval, this system like other locally delivered antimi-

crobbials is conventionally used as an adjunct to SRP in clinical practice.

One phase 4 or postmarketing trial investigated the use of doxycycline gel as an adjunct to SRP and demonstrated incremental benefits when the system was used in combination with SRP.<sup>28</sup> Accordingly, one arm of the adjunctive use trial involved initiating treatment with ultrasonic scaling plus doxycycline gel at baseline, and then isolated SRP at 3 months for those sites with residual pocketing (PD > 5 mm). The second arm of the study involved SRP alone at baseline, and then isolated ultrasonic scaling and doxycycline gel at those sites with residual pocketing. While both treatment strategies were equally effective at improving probing depths and clinical attachment levels over 6 months, responses were greater on average for the adjunctive doxycycline gel treatment at 3 months compared to SRP alone.

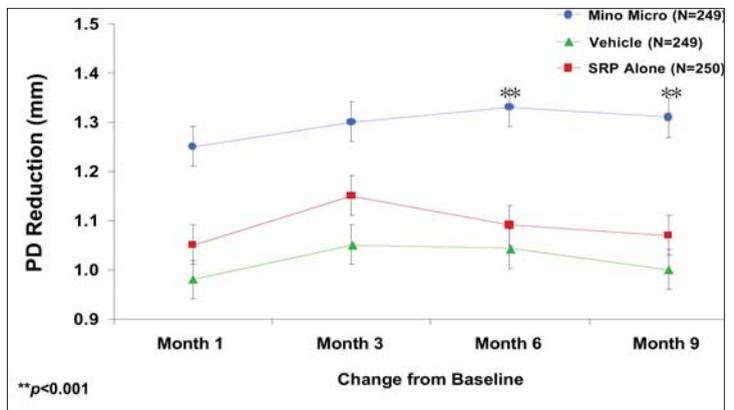
## Minocycline Microspheres

Arestin® (OraPharma, Inc., Warminster, Pa, USA) is an approved local delivery system featuring 1mg of minocycline hydrochloride microencapsulated in resorbable polymer microspheres (polyglycolide-co-dl-lactide). The delivery system (cartridge and syringe) is designed for quick and easy administration of one unit dose of Arestin subgingivally in periodontal pockets measuring  $\geq 5$  mm with bleeding on probing (BOP) (Figure 1). With this system, minocycline hydrochloride is maintained within pockets for 21 days at concentrations effective against periodontal pathogens. The agent may also block collagenases that are implicated in host tissue breakdown.<sup>29</sup>

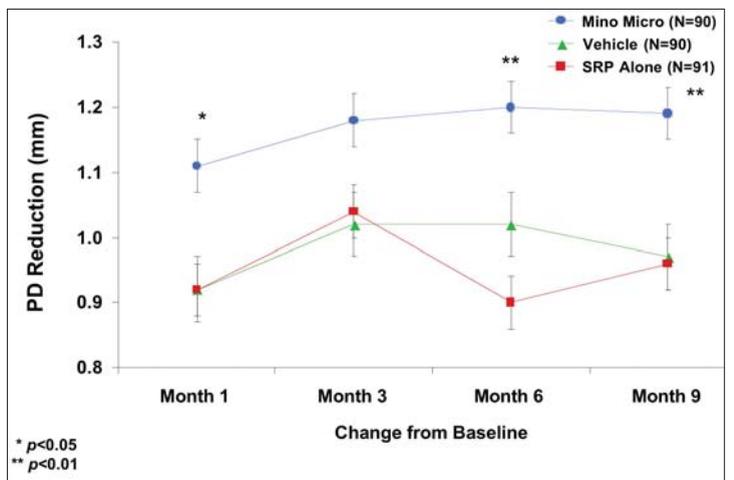


**Figure 1. Syringe handle and pre-measured cartridges for dispensing minocycline microspheres.**

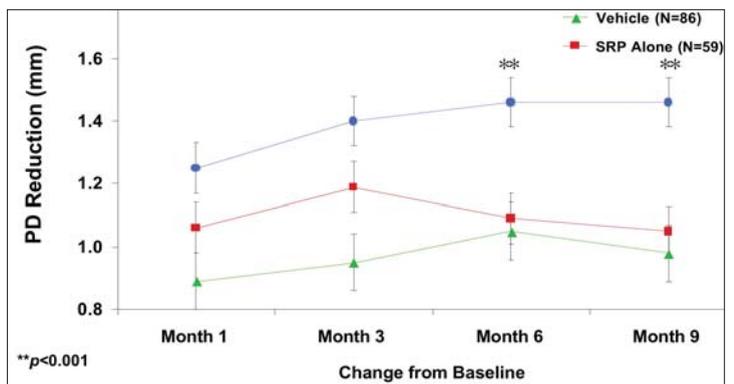
The pivotal clinical trials of minocycline microspheres involved approximately 750 subjects with generalized moderate to advanced chronic periodontitis recruited at 18 centers.<sup>30</sup> Periodontitis subjects meeting inclusion criteria at baseline were randomized to 1 of 3 treatments: 1) scaling and root planing (SRP) alone (positive control); 2) SRP plus polymer vehicle (placebo control); or 3) SRP plus minocycline microspheres. Full mouth probing exams were performed at baseline (prior to treatment) and at 1, 3, 6, and 9 months. Figure 2 graphs mean probing depth reductions observed in the 9-month trial for all subjects (intent-to-treat population) in the primary analysis. Analyses of covariance adjusting for centers indicated significant-inter-group differences in probing depth reductions at all time points ( $p < 0.001$ ). In particular, subjects treated with adjunctive minocycline microspheres exhibited significantly greater probing depth reductions as compared to control subjects treated with SRP alone. When smokers (Figure 3) or those with advanced periodontitis (mean baseline PD > 6 mm) (Figure 4), were considered in secondary analyses, again ANCOVA indicated significant probing depth reductions with adjunctive minocy-



**Figure 2. Mean probing-depth reductions over nine months for periodontitis subjects treated with adjunctive minocycline microspheres, adjunctive vehicle, or SRP alone. Adapted from Williams et al.<sup>30</sup>**



**Figure 3. Mean probing-depth reductions over nine months for periodontitis subjects who smoke and were treated with minocycline, adjunctive vehicle, or SRP alone. Adapted from Paquette et al.<sup>31</sup>**



**Figure 4. Mean probing-depth reductions over nine months for advanced periodontitis subjects (mean baseline probing depth  $\geq 6$  mm) treated with minocycline, adjunctive vehicle, or SRP alone. Adapted from Williams et al.<sup>30</sup>**

cline microspheres over control treatments.<sup>31</sup> Indeed, inter-group differences in PD reduction were greater among advanced periodontitis subjects versus the overall population.

A priori, a shift in subject mean probing depth < 5 mm with treatment was considered a clinically relevant and “maintainable” response. When regression analyses were performed comparing response odds with adjunctive minocycline microspheres treatment versus SRP alone, the odds ratios for subjects who smoked or who had advanced periodontitis were 2.06 (95% CI 1.10, 3.85) and 2.86 (95% CI 1.45, 5.66), respectively.<sup>32</sup> These data indicate that patients with advanced periodontitis or smokers are 2 to 3 times more likely to respond, and that this increase in odds is clinically relevant. Site analyses on pocket resolution (posttreatment PD < 5 mm) were also designated as meaningful. Again, a significantly and consistently higher percent of pockets were “resolved” with adjunctive minocycline microspheres versus SRP alone for all subjects and smokers, respectively (Table 2).<sup>33</sup>

A large, phase 4 (postmarketing) trial involving 2805 patients and 895 dentists

was conducted to evaluate the use of minocycline microspheres in private practices throughout the United States.<sup>34</sup> Accordingly, 1095 patients received 2 applications of minocycline microspheres (at baseline and 3 months) per protocol, and 1710 patients received only one minocycline microsphere application (at baseline). Mean 6-month pocket depth reductions were 1.82 and 1.94 mm for the patients receiving one and 2 minocycline microspheres treatments, respectively. Similar results were obtained in smokers, diabetic patients, and cardiovascular disease patients. After one minocycline microspheres treatment, 62% of sites had decreased to less than 5 mm, and after 2 treatments the corresponding proportion increased to 67%. This large private practice study demonstrated that minocycline microspheres plus SRP is effective in reducing pocket depth and that efficacy increased with retreatment (dose-response).

One recently published trial indicates that the effects of flap surgery may be enhanced with adjunctive minocycline microspheres treatment. Hellström and coworkers recruited 60 periodontitis patients and randomized them to either flap surgery plus minocycline micros-

pheres therapy (baseline and weeks 2, 3, and 5) or surgery alone.<sup>35</sup> At week 25, the mean PD reduction from baseline was 2.51 mm in the surgery plus minocycline microspheres (test) group versus 2.18 mm in the control group. Smokers in the test group had a significantly greater probing depth reduction (2.30 mm) as compared to smokers in the control group (2.05 mm). In addition, the number of sites with probing depth reductions of 2 mm or more was significantly higher in the test group than in the control group. Hence, minocycline microspheres may be adjuncts to both nonsurgical and surgical therapies for patients with moderate to severe, chronic periodontitis.

These efficacy findings for minocycline microspheres have been extended to peri-implantitis, an inflammatory process around one or more osseointegrated implants in function, resulting in a loss of supporting bone and associated with a similar pathogenic flora. Renvert and coworkers conducted a clinical trial in which 32 subjects with peri-implantitis (one implant with PD > 4 mm, bleeding and/or exudate on probing and the presence of putative pathogens) randomly received debridement plus minocycline

**Table 2.** Percentage of periodontal pockets resolving with adjunctive minocycline microspheres versus SRP. Adapted from Paquette et al.<sup>33</sup>

Baseline PD	5mm		6mm		7mm		>8mm	
	Mino Micro	SRP Alone	Mino Micro	SRP Alone	Mino Micro	SRP Alone	Mino Micro	SRP Alone
<b>Treatment All Subjects</b>								
Month 1	76 p<0.0001	69	47 p<0.001	39	22 p=0.31	20	10 p=0.24	8
Month 3	78 p<0.0001	71	52 p=0.01	48	28 p=0.01	23	19 p=0.02	14
Month 9	75 p<0.0001	66	54 p=0.0005	49	34 p=0.001	27	22 p=0.01	16
<b>Treatment Smokers</b>								
Month 1	73 p<0.0001	66	40 p=0.003	34	17 p=0.53	15	6 p=0.09	3
Month 3	74 p<0.001	66	44 p=0.17	41	22 p=0.04	15	16 p=0.003	5
Month 9	70 p<0.0001	61	45 p=0.006	39	27 p=0.04	20	20 p=0.04	12

microspheres or debridement plus chlorhexidine gel (0.2%) at baseline, 1 month, and 3 months.<sup>36</sup> While both treatments reduced putative pathogens, adjunctive minocycline microsphere treatment resulted in significant improvements in PD compared to chlorhexidine gel at 1 month, 3 months, and 6 months. Significant reductions in bleeding on probing were also noted for up to 12 months. This investigative group published the results from a second trial with 30 peri-implantitis subjects. Again, adjunctive minocycline microspheres improved PD and bleeding scores, whereas the adjunctive use of chlorhexidine gel had limited effects on bleeding scores.<sup>37</sup> Another investigative team, Salvi and coworkers, also noted consistent efficacy with minocycline microspheres for treating peri-implantitis.<sup>38</sup> Here, the investigators applied minocycline microspheres to implant sites exhibiting bone loss and PD > 5 mm following a 3-week debridement and hygiene interval. While 6 of 31 implants were either rescued or exited from the trial because of persistent peri-implantitis, all other implants (80.6%) showed significant reduction in both PD and BOP over 12 months with minocycline microspheres therapy. The investigators also examined peri-implant microflora using DNA-DNA checkerboard hybridization techniques and observed significant reductions in *A. actinomycetemcomitans* at 12 months and reductions in “red complex” bacteria (*T. forsythia*, *P. gingivalis*, and *T. denticola*) for 6 months.<sup>39</sup> Binary regression analysis showed that the clinical parameters and smoking history could not discriminate between successfully treated and rescued/exited implants at any observation time point. In addition, failures in treatment could not be associated with the presence of specific pathogens or by the total bacterial load at baseline. Collectively, these new data indicate improvements in the clinical signs of peri-implantitis over 12 months with adjunctive locally administered minocycline.

Goodson and coworkers conducted a clinical trial utilizing 124 subjects with

moderate to advanced chronic periodontitis. Subjects were randomly assigned to either SRP alone or minocycline microspheres and SRP. All patients received full-mouth SRP at baseline, followed by treatment with minocycline microspheres if assigned to the SRP and minocycline microspheres group. The examiner was blinded to the patient’s treatment. Clinical assessments were made and plaque samples were collected at baseline and at Day 30. The results demonstrated that adjunctive minocycline microspheres significantly reduced red-complex periodontal pathogens as compared to SRP alone by one month.<sup>40</sup>

Another investigation conducted by Oringer et al<sup>41</sup> investigated the effect of minocycline microspheres on gingival crevicular fluid (GCF) levels pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) and interleukin 1-beta (IL-1). ICTP is a bone-specific degradation product and IL-1 is a potent bone-resorptive cytokine. Forty eight periodontitis patients were randomized to receive SRP followed by minocycline microspheres or vehicle. Eight healthy individuals served as a control group. Results found a potent short term reduction of ICTP and IL-1 in the SRP plus minocycline microspheres group.

## Summary and Conclusions

Residual or persistent periodontal inflammation is associated with instability of dental tissues (periodontal disease progression and tooth loss). Cumulative data from clinical trials and meta-analyses support a complementary medical-mechanical model using locally delivered antimicrobials for treating chronic periodontitis. Overall, the clinical evidence accrued to date consistently shows that when locally administered antimicrobials are used adjunctively, significantly greater PD reductions and/or attachment level gains occur in patients. These responses are clinically relevant

because they are accompanied by a greater likelihood for patient maintenance or pocket resolution. Recent trials also indicate that locally administered antimicrobials may enhance the effects of periodontal surgical therapy and may reduce the signs of peri-implantitis. The consistency of these findings supports the use of locally administered antimicrobials for managing dental patients with chronic periodontitis.

## Clinical Implications

- Recent clinical trials indicate that locally administered antimicrobials may enhance the effects of periodontal surgical therapy and may reduce the signs of peri-implantitis.
- Patients with periodontitis exhibiting moderate (4-5mm) and deep ( $\geq 6$  mm) probing depths were 2 to 3 times more likely to exhibit alveolar bone loss over 10 years.
- A systematic review and meta-analysis demonstrated that adjunctive locally administered antimicrobials improved PD over SRP alone in chronic periodontitis patients.
- Patients with advanced periodontitis or smokers are 2 to 3 times more likely to respond to SRP + minocycline microspheres than to SRP alone.
- Use of minocycline microspheres has been shown to be advantageous when used as an adjunctive therapy to both nonsurgical and surgical therapies in patients with moderate to severe, chronic periodontitis.
- Adjunctive use of minocycline microspheres has shown a reduction in red-complex periodontal pathogens as compared to SRP alone.

## Disclosure

Dr. Paquette has served as a scientific consultant and investigator for OraPharma, Inc. Dr. Ryan and Ms. Wilder are scientific consultants for OraPharma, Inc.

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