Intraoral electrostimulator for xerostomia relief: a long-term, multicenter, open-label, uncontrolled, clinical trial

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Objective. A previous sham-controlled multinational study demonstrated the short-term efficacy and safety for xerostomia treatment of an intraoral device that delivers electrostimulation to the lingual nerve. The objective of this study was to test the hypothesis that those beneficial effects would be sustained over an 11-month period.

Study Design. The device was tested on a mixed sample of 94 patients with xerostomia in an open-label, uncontrolled, prospective multicenter trial. Statutory outcome assessments were done at 5th, 8th, and 11th months and analyzed by multiple comparisons.

Results. Improvements achieved at month 5 from baseline were sustained throughout the follow-up period for the primary outcome, xerostomia severity, and the secondary outcomes resting whole salivary flow rate, xerostomia frequency, oral discomfort, and difficulties in speech, swallowing, and sleeping. No significant side effects were detected.

Conclusions. The beneficial effects of a removable intraoral electrostimulating device were sustained for an 11-month period. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:773-781)

Xerostomia is the subjective sensation of dry mouth. This common symptom is multifactorial in origin but frequently associated with the same difficulties in swallowing, speaking, and sleeping. The prevalence for xerostomia has been reported to vary from 24% to 27% in women and from 18% to 21% in men. Because xerostomia is mostly induced by deficiency of saliva, an effective means to relieve it would be to stimulate the residual secretory capacity of the salivary glands by modulating the autonomic reflex arc that regulates salivation. Salivary secretion can be increased pharmacologically with systemic sialogogues, such as pilocarpine, but this carries the risk of annoying adverse events, such as sweating, flushing, increased urination frequency, and gastrointestinal complaints. Because of comorbidities in the older age group, sialogogue use is frequently contraindicated or adds to the inconvenience of managing already polymedicated patients. Xerostomia can be treated also by replacing lacking saliva with mouth rinses or moistening gels. These are safe, but their xerostomia-relieving effect is very short-lived, requiring frequent application, and no effect on salivary output has been demonstrated.

Recent proof-of-concept studies have shown that electrostimulation delivered by an intraoral device (GenNarino) is both a safe and an efficacious way of decreasing oral dryness. The latter study, which was crossover sham controlled, showed superiority of an activated device (delivering electrical and mechanical stimulation) over a sham device (delivering only mechanical stimulation). Further improvement in oral dryness was also verified when using the activated devices for a total of 5 months from the study start. The purpose of the present study was to continue for 6 additional months the evaluation of GenNarino in an open-label uncontrolled trial. We also sought to find out if the effect could be related to length of electrostimulation (1, 5, or 10 minutes). We hypothesized that the improvement obtained for xerostomia, the associated symptoms, and salivary output in the earlier study would be sustained, with no incidence of significant adverse effects and with no relationship to electrostimulation duration.

MATERIALS AND METHODS

Device description

GenNarino is an individualized mouthpiece containing an electronic circuit with a microprocessor, a pair of stimulating electrodes, and a 30-mA/h battery (Figure 1). The electrodes contact the oral mucosa in the mandibular third molar area, close to the lingual nerve. The electrical current is of low intensity and not felt by the patient.

Statement of Clinical Relevance

Xerostomia is difficult to treat owing to frequent treatment resistance. Moreover, for many sufferers who are polypharmacy patients, systemic cholinergic medication is inappropriate. Electrostimulation has the potential to be an effective alternative that addresses the shortfalls of the traditional therapeutic methods.
Study design
The present study constitutes the second part of a prospective trial lasting 11 months in total. The first part, including the 2-month active versus sham-controlled stage of the trial and a 3-month open-label follow-up period using active devices only, has already been published.\(^9\) The present study describes the open-label follow-up period of those patients that remained in the second part of the trial lasting 6 additional months. The entire 9-month open-label uncontrolled stage of the trial was divided into 3 consecutive 3-month periods. For this stage, the study coordinator randomly (using a computerized randomized allocation system) allocated subjects to wear the device for either 1, 5, or 10 minutes at a time, during the periods of months 3-5, 6-8, and 9-11. Subjects were instructed to use the device as many times as they liked but not more than once every hour.

The trial has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002) and the additional requirements of Internal Review Boards in each country where the research was carried out. Written informed consent was obtained from each participant. The trial has been registered at http://ClinicalTrials.gov, identifier: NCT00509808 (http://clinicaltrials.gov/ct2/show/NCT00509808). Patients were recruited in 14 institutions of 13 countries (see authors’ affiliations). Patients were eligible for the study if they had xerostomia. Excluded were those <18 years old; patients with human immunodeficiency virus or hepatitis C virus infection or other severe diseases (except chronic graft-vs.-host disease [GVHD]); patients using anticoagulants, pacemakers, or defibrillators; subjects with allergies to materials used in GenNarino; patients suffering from mental disease or depression; pregnant women; subjects suffering from chronic or recurrent, erosive or ulcerative, or potentially malignant or malignant oral lesions; individuals displaying oral anatomic characteristics precluding the use of GenNarino (e.g., very limited mouth opening); and persons showing poor oral hygiene (i.e., presence of heavy deposits of dental plaque).

Outcome measures
The devices were manufactured by the study initiating company, Saliwell (Harutzim, Israel), using impressions taken from the subjects’ dental arches. After baseline, outcome assessments took place at the end of the 5th, 8th, and 11th months of device use. At each follow-up, questionnaires, whole saliva, and safety-related information were collected. The primary outcome (xerostomia severity) and patient-centered secondary outcomes were measured by a previously validated questionnaire.\(^{10,11}\) Answers to 5 questions were reported with the use of 100-mm-long visual analog scales (VAS) running from the worst condition on the left to the best on the right end of the line. Questions were: “How dry is your mouth today?” (for the primary outcome, hereinafter “dry severe”); “How comfortable is your mouth today?” (“discomfort”); “How difficult is it for you to speak because of your dry mouth?” (“speech”); “How difficult is it for you to swallow because of your dry mouth?” (“swallow”); and “How do you rate your quality of life today?” (“QoL”). Three additional questions were included: first, “How often does your mouth feel dry?” (“dry frequent,” with possible responses: always/frequently/occasionally/never, rated 1/2/3/4, respectively); second, “During the past week, how many times on average did you wake up in the night due to dryness of your mouth?” (“wakeup”); and third, “How often every day did you use the device”? Other secondary outcome measures were resting and mastication-stimulated whole salivary flow rates (RSFR and SSFR, respectively), which were assessed at morning hours always. Patients were requested to take nothing into their mouth for 90 minutes or longer, and then to spit during 5 minutes into containers (F. L. Medical, Padova, Italy; cat. no. 25,174) while avoiding swallowing. The containers were closed immediately after collection to avoid fluid evaporation. Salivary flow was stimulated by chewing a piece of parafilm. Saliva volume was determined gravimetrically (assuming a specific gravity of 1).\(^{12}\)

As safety-related secondary outcome measures, vital signs (blood pressure and heart rate), changes in health condition (as reported by the patients), and oral mucosal status were assessed.

Statistical methods
Based on an earlier study of an antixerostomia agent,\(^{13}\) a sample size of 72 subjects was calculated to be necessary to detect a difference of 11 points on a VAS with a SD of 13 for a 2-sided test with 95% power and a 5% level of significance.\(^{14}\) Because the primary aim of the study was to assess whether the 5-month treatment effects were maintained for an additional 6 months of GenNarino use, the total number of subjects to be recruited was 110, assuming an attrition rate of 35%.

Statistical analysis involved 4 models for each one of the 9 outcome variables, for a total of 36 fitted models. In particular, 4 models considered the following covariates: 1) length of device application at 5 months’ follow-up (covariate with 3 categories: 1, 5, and 10 minutes); 2) length of device application at 8 months’ follow-up (covariate with 3 categories: 1, 5, and 10 minutes); 3) length of device application at 11 months’ follow-up (covariate with 3 categories: 1, 5, and 10 minutes); and 4) time period (covariate with 4 categories: baseline, 5 months, 8 months, and 11 months). In
case of quantitative outcomes (all except “wake-up” and “dry frequent”), the mixed model was used; for skewed outcomes (RSFR and SSFR), the natural logarithm was chosen as link function. For the count outcome “wake-up” the random-effects Poisson model was fitted. For the ordinal outcome “dry frequent” the cumulative link mixed model was used.

Several covariance structures were applied: compound symmetry, unstructured, and autoregressive. The most appropriate model was chosen according to Akaike’s information criterion. The Bonferroni correction was applied for multiple paired comparisons between lengths of device use. Statistical analysis was performed with the use of PROC MIXED in SAS for Windows, version 9.1. For the count and ordinal outcomes, the glamm function of Intercooled Stata version 9.0 was used. The hypotheses were tested at a 5% 2-sided level of significance.

The variables at baseline, 5-month, and 8-month assessments were compared between the groups of individuals that completed the study with those that were lost to follow-up, with the use of the t test for equal or unequal variances as appropriate. The \( \chi^2 \) test was applied for the variable “dry frequent.” Statistical analyses were performed by coauthors D.M. and G.R.B.M.

RESULTS

As shown in Figure 2, a total of 114 patients were evaluated from December 2006 to November 2009. Of the 94 patients allocated to the entire open-label study, 81 (86%) remained in the second, presently reported, part of the study. Seventy (74%) and 56 (60%) subjects completed follow-up until the end of months 8 and 11, respectively. Loss to follow-up (n = 38) during the open-label study was either patient initiated (n = 22; 23%) or not (n = 16; 17%). Regarding the former, patients withdrew themselves from the trial owing to lack of satisfaction with GenNarino (n = 7), adverse events not related to the device (n = 7), or other reasons (n = 8), which are detailed in Figure 2. Regarding the latter, intervention was discontinued because of device malfunction or battery draining (n = 6) or withdrawal of centers from the trial after the expiration of funding grants or logistical difficulties (n = 10). Patients’ baseline, 5-month, and 8-month values were not different between those who completed the 8- and 11-month follow-ups and those that dropped out, although SSFR tended to be initially higher among those who completed the study (\( P = .07 \)). The distribution of diagnoses among the subjects who completed the study was similar to that at baseline (all \( P > .4 \)): Sjögren syndrome (SS) (66% vs. 60% at baseline), radiotherapy to the head and neck (7% vs. 10%), use of

Fig. 2. Subject flow diagram. AE, Adverse events.
medications (9% vs. 8%), GVHD (2% vs. 4%) and other or idiopathic reasons (16% vs. 18%).

As shown in Table I, the mean age of participants was 59 years (range 19-78 years), and the majority (81%) were women. The diagnostic groups generally shared similar patterns. Notably, "dry severe" and "dry frequent" were similar in all groups, patients suffering from xerostomia due to radiotherapy had lower salivary flow rates, and those with GVHD had fewer problems with speaking, swallowing, and awakening.

At 5- and 8-month follow-ups, subjects reported equivalent average daily cumulative length of device usage of 21 minutes, ranging from 1 minute (1 time per day for 1 minute each time) to 150 minutes (e.g., 15 times per day for 10 minutes every time). At month 11, the average self-declared length of daily use decreased to 18 minutes.

**Efficacy**

The preselected outcome measures for the follow-up assessments as subgroups of length of use (1, 5, and 10

### Table I. Description of patient characteristics at baseline for the subjects that were allocated to the entire open-label, uncontrolled stage of the trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All subjects</th>
<th>SS Radiotherapy</th>
<th>Medications</th>
<th>GVHD</th>
<th>Other/idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>94</td>
<td>56</td>
<td>9</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>female</td>
<td>81%</td>
<td>93%</td>
<td>33%</td>
<td>88%</td>
<td>0%</td>
</tr>
<tr>
<td>Age, y</td>
<td>59</td>
<td>61</td>
<td>53</td>
<td>59</td>
<td>51</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Diagnosis (% of subjects)</td>
<td>100%</td>
<td>60%</td>
<td>10%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Dry severe*</td>
<td>33</td>
<td>33</td>
<td>37</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>SD</td>
<td>24</td>
<td>23</td>
<td>30</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Dry frequent†</td>
<td>1.7</td>
<td>0.7</td>
<td>1.7</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Discomfort*</td>
<td>37</td>
<td>38</td>
<td>34</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>Speech*</td>
<td>48</td>
<td>43</td>
<td>49</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>Swallow*</td>
<td>42</td>
<td>37</td>
<td>29</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Wake-up‡</td>
<td>2.0</td>
<td>1.9</td>
<td>2.8</td>
<td>2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>QoL*</td>
<td>56</td>
<td>53</td>
<td>58</td>
<td>60</td>
<td>77</td>
</tr>
<tr>
<td>RSFR</td>
<td>63</td>
<td>49</td>
<td>12</td>
<td>66</td>
<td>108</td>
</tr>
<tr>
<td>SSFR</td>
<td>10–198</td>
<td>10–161</td>
<td>0–53</td>
<td>29–232</td>
<td>91–181</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>223</td>
<td>147</td>
<td>82</td>
<td>393</td>
<td>648</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>79</td>
<td>78</td>
<td>80</td>
<td>79</td>
<td>75</td>
</tr>
<tr>
<td>Heart rate</td>
<td>73</td>
<td>73</td>
<td>74</td>
<td>76</td>
<td>65</td>
</tr>
</tbody>
</table>

SS, Sjögren syndrome; GVHD, graft-vs.-host disease; QoL, quality of life; RSFR, resting salivary flow rate (μL/min); SSFR, stimulated salivary flow rate (μL/min); BP, blood pressure (mm Hg).

*VAS score (from 0 (worst situation) to 100 (best situation)).
†1 (always), 2 (frequently), 3 (occasionally), or 4 (never).
‡Times per night.
minutes) showed no statistically significant intersubgroup differences except for SSFR, which at month 5 was higher for 1-minute versus 5- or 10-minute usage (data not shown). The data were therefore pooled for the multiple comparison analysis. As shown in Table II, time effect was statistically significant for all of the outcome variables except QoL. The effect reached at month 5 for variables “dry severe,” “dry frequent,” “discomfort,” “speech,” “swallow,” “wake-up,” and RSFR and at month 8 for SSFR were sustained until month 11. Most clinically important, 8 patients started the study with no RSFR or SSFR. Their dryness severity score doubled after 8 months, and in 7, saliva could be collected on at least 1 follow-up visit.

Safety
No significant changes in the vital signs were detected. The maximal frequency of oral mucosal findings was 8% at the 5-month visit and declined thereafter. They consisted of redness, aphthae, or postrauamtic lesions resulting from tooth extraction or biting. In all cases except one, the location of those lesions was not related to the device bearing area.

DISCUSSION
Our data verify the hypothesis that the improvement obtained for xerostomia, the associated symptoms, and salivary output on the first part of the study would be sustained for the long term regardless of length of device use at a time. In the previous proof-of-concept, prospective, double-blind, crossover, sham-controlled, 2-month-long stage, the active (electrical and mechanical stimulation) performed significantly better than the sham (mechanical stimulation only) device to improve dryness severity and frequency and swallowing difficulty. Thereafter, the data obtained after 5 months of active use of the device, had shown that most parameters improved, except for global “QoL,” swallowing difficulty, and SSFR. Those results were encouraging, but did not guarantee a sustained positive effect of the device. Indeed, other studies have reported poor patient adherence to long-term use of removable intraoral ap-

**Table II. Multiple comparison analysis when pooling together the 1, 5, and 10-minute groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 5</th>
<th>Month 8</th>
<th>Month 11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome measure per outcome assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Multiple comparison between lengths of use (P value</em>)</em>*</td>
<td>Month 5 vs.</td>
<td>Month 8 vs.</td>
<td>Month 11 vs.</td>
<td>Month 8 vs.</td>
</tr>
<tr>
<td></td>
<td>baseline</td>
<td>baseline</td>
<td>baseline</td>
<td>month 5</td>
</tr>
<tr>
<td>Dry severe</td>
<td>Mean</td>
<td>35</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>24</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Dry frequent</td>
<td>Mean</td>
<td>1.8</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.7</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Mean</td>
<td>39</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>25</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Speech</td>
<td>Mean</td>
<td>50</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>27</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Swallow</td>
<td>Mean</td>
<td>43</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>29</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Wake-up</td>
<td>Mean</td>
<td>1.8</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.4</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>QoL</td>
<td>Mean</td>
<td>57</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>22</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>RSFR</td>
<td>Median</td>
<td>56</td>
<td>67</td>
<td>78</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>11–193</td>
<td>30–257</td>
<td>18–337</td>
<td>20–263</td>
</tr>
<tr>
<td>n</td>
<td>56</td>
<td>56</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>SSFR</td>
<td>Median</td>
<td>344</td>
<td>309</td>
<td>363</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>22–880</td>
<td>72–866</td>
<td>60–875</td>
<td>68–1022</td>
</tr>
<tr>
<td>n</td>
<td>55</td>
<td>56</td>
<td>55</td>
<td>48</td>
</tr>
</tbody>
</table>

Abbreviations and notes as in Table II.
*Bonferroni adjusted.
Side effects were frequent and significant in 84% of the cases. Sublingual responsiveness to pilocarpine. Systemic feeling of oral dryness, speaking, chewing, and swallowing a mixed sample of xerostomia patients improved the placebo, and no significant side effects were registered. Compared with those 2 systemic dialogue studies, the beneficial effect achieved here after a comparable period of 8 months was not inferior. The safety profile in our study was limited to mild local mucosal changes. Our drop-out rate of 26% after 8 months was similar to those of the trials with pilocarpine (21% after 5 months) and interferon (23% after 6 months).

Another shortcoming of this study is the heterogeneity of the subject population. However, although xerostomia may be caused by a variety of conditions, the symptom is basically common to all the sufferers. Treatment is nonspecific, with the same therapeutic agents and techniques being applied in all cases.26

We were also interested in comparing electrostimulation with other xerostomia therapies delivered during a similar period of time. In systematic reviews of the literature on therapies for xerostomia,26–29 2 definitive long-term self-administered treatments and follow-up trials stand out. Fox et al. (1991)5 reported that 5-mg pilocarpine capsules given 3 times daily for 5 months to patients with residual salivary secretory potential.31,32 Of special note, however, is the fact that among some of our patients with no collectable saliva at the beginning of the study, saliva could be collected in follow-up visits. Our interpretation is that failure to collect saliva does not necessarily mean that salivary gland function has ceased completely and permanently.

That being said, an alternative interpretation would be that our study suffers from possible “demand characteristic bias.”33 That occurs when a participant picks up on some clue from the researcher that gives him an idea of what type of response the researcher is looking for. Thus, the subjects in the long-term study had participated in the previous sham-controlled one where most of them perceived that the electrically active GenNarino was effective. Guarding against that bias was the fact that not only self-perceived parameters, but also that the objective outcome measures (RSFR and SSFR) improved. Further, not all self-assessed parameters improved, the significant exception being the overall QoL. The reason for this apparent discrepancy could be explained by the presence of other quality of life–impairing conditions in addition to xerostomia, such as ocular dryness and various complications of SS or of comorbidities, which are common among aged individuals.34–36

On one hand, intra- and extraoral electrostimulation on the salivary gland area has been reported to increase salivary production and relieve symptoms of dry mouth.5,9,37–39 On the other hand, any electrophysiologic effect depends on a stimulation intensity high enough to induce impulses in the nerve of interest.40,41 The first important factor in achieving the stimulation threshold is the distance between the nerves and the stimulating electrodes. To this end, when the device is manufactured, the electrodes are placed close to the estimated location of the lingual nerve, but the actual distance may vary from 1 to 4 mm,42 limiting the control over the stimulating strength.

The second important feature of threshold is that it varies inversely with the fiber diameter.40,41 Based on its electronic design features, GenNarino is likely to evoke the salivary reflex primarily through excitation within the lingual nerve of: 1) the large A beta fibers which relay modalities of touch-pressure, vibration, and possibly proprioception, and 2) the efferent secretomotor autonomic fibers to the submandibular and sublingual salivary glands, which are relayed from the facial nerve via the chorda tympani.43–46

The third feature is the length of stimulation. Its clinical impact may be negligible, as suggested by our results. However, it was impossible to ascertain...
whether the subjects were able to comply rigorously with the randomized assignment of 1, 5, or 10-minute duration for each session.

It has been postulated that in the long run, electrostimulation augments normal physiologic salivary reflexes. A study on the effect of transcutaneous nerve stimulation on radiotherapy-induced xerostomia reported increase in citric acid–primed salivary production lasting longer than the length of treatment delivery. Therefore, long-term administration of electrostimulation could reset the salivation reflex, which would become more reactive to all kinds of stimuli, either related or not to electrostimulation. Additionally, earlier studies suggested that stimulation of the salivary reflex arch might increase the release of nonadrenergic noncholinergic tropic mediators and antiapoptotic stimuli, which lead to regeneration of salivary functional tissue.

This assumption was based on studies that demonstrated mitogenic responses in rat parotid and submandibular glands after electrical stimulation of their parasympathetic nerves. Future controlled investigations into the specific electrophysiologic target and molecular effects of GenNarino on the gland function and on the composition of the saliva are warranted. The role of changes in salivary composition could be significant, because the changes in salivary output were small. Nevertheless, according to Sreebny and Valdini, “little saliva is needed to overcome the feeling of oral dryness.”

In conclusion, GenNarino appears to be an effective, acceptable, and safe tool to treat xerostomia of various causes, although well controlled trials, evaluating inter alia negative outcomes, such as patient attrition, are warranted to study long-term efficacy. Many potential users are elderly and heavily medicated. Current pharmacologic treatments have a high incidence of side effects. Using a device such as Gennarino to treat xerostomia would thus appear to be more appealing to patients as well as physicians to not increase the risks of polypharmacy.

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