Snus as a Smoking Cessation Aid: A Randomized Placebo-Controlled Trial

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Received July 1, 2011; accepted August 18, 2011

Abstract

Introduction: Snus is a low-nitrosamine smokeless product that appears to be safer than other smokeless products. Evidence indicates that snus has been used as an effective smoking cessation aid in Scandinavia. No randomized controlled trial has directly tested the efficacy of snus for smoking cessation.

Methods: This randomized, double-blind, placebo-controlled multicentre trial tested the efficacy of snus for smoking cessation. Of the 250 subjects, 125 were randomized to active or placebo snus sachets. Subjects were followed up through 28 weeks after randomization. In total, 5 clinical visits and 8 telephone contacts were scheduled. Primary outcome measure was biologically verified continuous smoking abstinence from Week 6 through 28.

Results: The continuous abstinence rate during Weeks 6–28 in the snus and placebo groups was 4.0% and 1.6% (odds ratio [OR]: 2.5, 95% CI: 0.4–27), respectively. The point prevalence abstinence rate at 6 weeks was 18.4% in the snus group versus 8.8% in the placebo group (OR: 2.3, 95% CI: 1.1–5.0, p = .03). At Week 28, the difference in favor of the snus group was not statistically significant (12.8% vs. 7.2%, OR: 1.9, 95% CI: 0.8–4.4). Snus was generally well tolerated. Treatment-related adverse events were more common in the snus group were generally mild and included nausea, dyspepsia, gingivitis, hiccups, and dizziness.

Conclusions: Although the cessation rates generally were low and, at 28 weeks, did not differ between active and placebo, early quit rates suggested that snus was superior and with similar effect sizes to those with nicotine replacement. These results suggest that snus needs to be further researched as a smoking cessation treatment.

Introduction

Tobacco-related disease is the leading cause of preventable death in much of the developed world, accounting for an estimated one in every five deaths (Peto, 1994). In addition, tobacco-related diseases are rapidly increasing in the developing countries. Half of all long-term regular smokers die from tobacco use, and 50% of these die prematurely during middle age, losing some 20–25 years of life expectancy compared with nonsmokers (Peto & Lopez, 2000).

Several medications have been shown to double or triple the odds of smoking cessation (Aubin, Karila, & Reynaud, 2011). However, these medications are relatively expensive plus many smokers have misperceptions about nicotine medications. One possible alternative for smoking cessation is the tobacco product snus.

Several correlational lines of evidence suggest that snus can aid in smoking cessation. In a recent review, all seven studies in Norwegian men that examined smoking status as a function of snus use found that quit rates were higher among those with snus experience and highest among current snus users (Lund, Scheffels, & McNeill, 2011). Among Norwegian men, snus is the most common smoking cessation product and is also associated with better long-term results than nicotine replacement (NR; Lund, McNeill, & Scheffels, 2010).

In Swedish studies, the same pattern is seen. In one study among men who had tried to give up smoking with some aid, a majority (58%) had used snus as an aid to stop, and those using snus had higher quit rates than those using NR. This was also true for women, although much fewer of them used snus (Ramström & Foulds, 2006). In a regional survey, 30.4% of men and 14.8% of women had used snus as a smoking cessation tool (Lindström, 2007), and having used snus at the latest quit attempt increased the probability of being abstinent by about 50% (Gilljam & Galanti, 2003).

Although these correlational data are encouraging, so far there has been no randomized controlled trial (RCT) of snus as a smoking cessation aid, and most scientists and clinicians (e.g., Hatsukami, Lemmonds, & Tomar, 2004) and health agencies (e.g., European Union; Scientific Committee on Emerging and Newly Identified Health Risks [SCENIHR], 2008) have asked for placebo-controlled RCT with similar designs to those used...
to market NR products. One prior uncontrolled study with a nonsnus smokeless product found encouraging results in highly dependent smokers (Tilleshalski, Rodu, & Cole, 1998), and one RCT but without a placebo tested a nonsnus Danish smokeless product with good short-term efficacy but no statistically significant long-term efficacy (Tornesen, Mikkelsen, & Bremann, 2008).

A concern about use of snus is that it might have greater health risks than NR (Kotlyar et al., 2010). However, in recent reviews, the harm from snus has been suggested to be at most 10% to that of smoking (Levy, Mumford, & Cummings, 2004; Royal College of Physicians, 2007), and it is unlikely that a brief use of snus (e.g., for 16 weeks) would be of any significant long-term harm.

The major purpose of the current study was to provide a placebo-controlled trial of snus for smoking cessation. Since some have questioned whether the Swedish experience would be replicable in other countries (SCENIHR, 2008), we examined the efficacy of snus in non-Scandinavian smokers. A secondary aim was to examine the safety and tolerability of snus as a brief smoking cessation aid.

## Methods

### Study Design

Daily smokers were recruited into this double-blind, placebo-controlled, randomized, multicentre parallel-group clinical trial conducted at five trial sites located in the United States (see “Acknowledgments”). The primary objective was to examine the ability of snus to increase the quit rate measured as the continued cessation rate during Week 6 through 28 documented by participants and confirmed by expired-air carbon monoxide (CO) less than 8 ppm. Secondary outcome measures included continued cessation during Week 6 through 16 (i.e., during active treatment) and 1-week point prevalence cessation at Weeks 6, 16, and 28. Other secondary objectives were to assess the safety and acceptability of snus as evidenced by the frequency of adverse events (AEs) and compliance to allocated treatment.

The study was conducted by a Clinical Research Organization (Covance) from February 2009 to March 2010 (ClinicalTrials.gov identification number: NCT00843622). The trial sites were clinical research centers focused on conducting Phases 1–4 clinical trials. None of the centers had previous experience with smoking cessation interventions.

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2008) and in compliance with the institutional review boards and independent ethics committees at each of the study sites and the International Conference on Harmonisation and Good Clinical Practice Guidelines (International Conference on Harmonisation, 2009). All participants gave written informed consent prior to randomization and any study procedures.

After randomization, participants were dispensed their allocated study product and were instructed to use it for 4 weeks before the target quit date. Such pretreatments of medication appear to aid smoking cessation (Stead, Perera, Bullen, Mant, & Lancster, 2008). They were then instructed to use the study product for another 12 weeks, with tapering of product use during the last 3 weeks. Posttreatment follow-up continued through 28 weeks after randomization.

### Participants

Subjects were identified from the research organization’s databases of potential volunteers and/or through advertisements in local media.

Subjects were included if they were:

1. male or female between 25 and 65 years of age. If female, they had a negative urine pregnancy test and were not lactating or had not been of childbearing potential for at least three months prior to use of study product.
2. smoking >9 cigarettes per day.
3. daily smokers for at least a year.
4. motivated to quit smoking with the help of a smokeless tobacco alternative.
5. in good general health as evidenced by medical history and physical examination.
6. practicing oral hygiene (brushing teeth once per day and regular dental checkups).
7. in a stable residence and had a telephone.

Subjects were excluded if they:

1. were current user of smokeless tobacco (past ST use was not an exclusion), used nicotine replacement therapy (NRT) or other nonprotocol treatments for smoking cessation, or unable to refrain from noncigarette tobacco other than assigned trial product during the study.
2. if female, were pregnant or lactating.
3. had oral conditions that could potentially have been made worse by use of study product.
4. had used any type of pharmaceutical or other product for smoking cessation within the past three months.
5. had a history of clinically significant renal, hepatic, neurological, and chronic pulmonary disease or a history of cardiovascular disease, including myocardial infarction within the last three months, significant cardiac arrhythmias, or poorly controlled hypertension that, in the judgment of the investigator, precluded participation.
6. had a history of alcohol or substance abuse within the past year.
7. resided in a household where another member was currently participating in the study.

### Interventions

With stratification by center, a predefined, central computer-generated randomization sequence assigned participants to receive snus or matching placebo in a 1:1 ratio at the baseline visit. Randomization was done by consecutively associating each included participant’s identifiers with a unique computer-generated sequential number. Lists at the study sites linked these numbers to specific study products, that is, snus or placebo snus. All study products were identified solely by identification numbers, which ensured that both participants and investigators were blinded to treatment assignments. The protocol did not include procedures to assess the success of the blinding.

The products were manufactured by Swedish Match AB according to the GothiaTek standard (Rutqvist, Curvall, Hassler,
Ringberger, & Wahlberg, 2011) and were supplied in identical food-grade plastic containers. The products came in sachets (pouches) that were placed in the anterior part of mouth between the upper gingiva and cheek for 30–60 min. The participants could choose between two different sachet sizes (0.5 or 1.0 g).

Swedish snus according to the GothiaTek standard is a low-nitrosamine, moist oral tobacco product with a water content of approximately 45%–55% and a pH of approximately 8.5. The nicotine delivery and uptake from snus sachets was described previously (Lunell & Lunell, 2005). The placebo products were almost identical to the snus products in physical appearance, mouth feel, pH, flavoring, and other sensory characteristics, but they did not contain tobacco or nicotine.

The sachets were to be placed under the upper lip and should not be chewed. Because of the relatively high pH, the participants often felt a slight burning sensation at the location of the sachet.

The dose and number of sachets consumed per day were determined by the participants. Subjects were instructed to use the sachets ad libitum, with a recommended maximum dose of 30 large sachets for those who smoked more than 15–20 cigarettes per day or had a Fagerström score of 7 or higher. Participants were informed that one large sachet typically could replace one cigarette. When subjects felt or expected an urge to smoke, they were instructed to try their allocated study product for at least 15–20 min. Subjects were not given a minimum number of sachets to use but were instructed to replace as many cigarettes as possible. Subjects were instructed to quit smoking at the latest by the end of Week 4. Participants continued the use of product until Week 14 and then cut down on product use during Weeks 14–16. The participants were instructed to document on a weekly basis in a diary how many cigarettes they smoked and how many study products they had used on average per day.

If a subject had quit with the help of their allocated study product and there was an imminent danger of smoking relapse during follow-up, they were informed that use of NRT or a smokeless tobacco product was a better option than a smoking relapse. However, no such products were dispensed.

At each clinic and telephone visit, subjects were provided with brief counseling by a research nurse that lasted 5–10 min, following Agency for Healthcare Research and Quality guidelines (U.S. Public Health Service, 2011). In addition, subjects were provided with an education booklet (the National Cancer Institute’s “Cleaning the Air” booklet) prior to randomization.

Subjects were informed that nicotine overdose could occur with excessive use of the product, particularly with concomitant smoking, but that symptoms (typically nausea, tachycardia, etc) would subside upon cessation of smoking or use of the product.

Assessments
The baseline visit was followed by clinical visits scheduled after Weeks 6, 10, 16, and 28. Participants were also contacted by telephone after Weeks 1, 2, 3, 4, 8, 13, 20, and 24.

The follow-up clinical visits included assessment of CO in exhaled air, self-reported smoking status, study product usage based on the participant’s diary information, AEs, and vital signs. A complete physical examination including an oral examination was done at the screening visit and at Weeks 16 and 28.

Blood tests were taken at the baseline visit and at the Weeks 6, 16, and 28 clinical visits to permit exploratory analyses of biomarkers related to tobacco exposure. The Minnesota Nicotine Withdrawal Scale (MNWS) instrument (self-report scale) was administered at baseline and at all clinical follow-up visits. Biomarker data or MNWS results are not reported in this paper.

Statistical Analysis
Measurement of abstinence, biochemical verification, and statistical analyses was done according to recommendations by the Society for Nicotine and Tobacco (Hughes, Benowitz, Hatsukami, Mermelstein, & Shiffman, 2004). Missing responses or missing data related to smoking status in diary would have been interpreted as though the subject had smoked on that occasion. Missing responses to nonabstinence questions were imputed by using the last observation carried forward method. All randomized individuals were included in all analyses, which were done on the basis of “intention-to-treat (ITT).” The compliant population was defined as those within the ITT population using one or more sachets per day during Weeks 1–6. Missing data at one timepoint except at Week 28 was allowed.

We assumed a continuous abstinence rate of 12% in the placebo group and 27% in the active snus group. A two-group continuity corrected chi-square test with a 0.05 two-sided significance level had 80% power to detect the difference between the active and placebo groups when the sample size in each group was 122 (total sample size of 244; Fleiss, 1981). The study was therefore intended to include a total of 250 subjects. Participants who discontinued the study were classified as smokers for the remainder of the study. The relationship of baseline variables and point prevalence smoking cessation at Weeks 16 and 28 was assessed using logistic regression models, including the baseline parameters, allocated treatment, and interaction terms. Models were built by using stepwise selection of explanatory variables with a significance level of <0.1 for a variable to stay in the model. The tested baseline parameters were age, body mass index, gender, ethnicity/race, age at smoking initiation, Fagerström Test for Nicotine Dependence score, previous use of smokeless tobacco, previous quit attempts with NRT, previous quit attempt without NRT, and total number of quit attempts.

Results
Of 485 potential participants screened, 250 were included in the trial and were randomly allocated to receive either snus or placebo (125 each). Most screen failures were due to poor health. One hundred and fifty-two participants (61%) completed the study (Table 1). Completion was defined as providing data at Weeks 16 and 28.

Participant Characteristics
Participant characteristics at baseline were comparable between the treatment groups (Table 2). The only statistically significant difference was that nonpharmacological smoking cessation aids had been used by 27 participants (21%) allocated to snus compared with 10 participants (8%) in the placebo group (p < .05).
Table 1. Participant Disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Snus (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>125 (100.0)</td>
<td>125 (100.0)</td>
</tr>
<tr>
<td>Completed study</td>
<td>82 (65.6)</td>
<td>70 (56.0)</td>
</tr>
<tr>
<td>Discontinued due to adverse event</td>
<td>5 (4.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Terminated by sponsor</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Participant withdrew</td>
<td>23 (18.4)</td>
<td>37 (29.6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (8.8)</td>
<td>13 (10.4)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.2)</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

Table 2. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Snus group (n = 125)</th>
<th>Placebo group (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Female, %</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Mean weight, kg</td>
<td>66.3</td>
<td>67.1</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Average no. of smoked cigarettes per day, M</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Previous use of smokeless tobacco (%)</td>
<td>6 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>No. of previous quit attempts, M (range)</td>
<td>2 (1–30)</td>
<td>2 (1–50)</td>
</tr>
<tr>
<td>Previous NRT exposure (%)</td>
<td>68 (54)</td>
<td>57 (45)</td>
</tr>
<tr>
<td>Previous exposure to other pharmaceutical smoking cessation products (%)</td>
<td>84 (67)</td>
<td>77 (61)</td>
</tr>
<tr>
<td>Previous exposure to cessation aids other than pharmaceuticals (%)</td>
<td>27 (21)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>FTND score, M</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Note. FTND = Fagerström Test for Nicotine Dependence; NRT = nicotine replacement therapy.

There was no statistically significant difference between the treatments groups for any of the characteristics except for previous exposure to cessation aids other than pharmaceuticals for which p < .05.

Study Product Usage

According to the participants’ diary data, the study product usage was relatively limited. Participants in the snus group who used 1.0 g sachets consumed on average three to four sachets per day. The corresponding number for those who preferred the 0.5 g sachets was four to eight sachets per day. Those allocated to placebo generally consumed a slightly higher number of sachets per day compared with the snus group, particularly during the first four to six weeks of the study. There was no statistically significant relationship between amount of product use and cessation outcome (data not shown).

Efficacy

The overall efficacy in stopping smoking was low with only 4.0% and 1.6% continuously abstinent during Week 6 through 28 for snus and placebo, respectively (Table 3). Statistically significant advantage for snus over placebo occurred for point prevalence outcomes at Weeks 6 and 16. Otherwise, the cessation rates were not statistically significantly different between the treatments (Table 3). For compliant subjects, the abstinence rates were one or two percentage points higher than for the ITT population. The point prevalence rates for snus and placebo among compliant participants were at 6 weeks 21% versus 10%, p < .04; at 16 weeks 19% versus 9%, p < .05; and at 28 weeks 15% versus 8%, nonsignificant. The logistic regression analyses of possible relationships between baseline variables and point prevalence cessation at Week 16 indicated that the only predictive variable was low number of cigarettes smoked per day in the past year. Similar analyses at Week 28 suggested that previous use of smokeless tobacco was associated with a higher cessation rate. There were no statistically significant interactions between any of the tested baseline variables and allocated treatment, that is, there was no evidence that the effect of snus was different in any subset of participants.

Adverse Events

Snus was generally well tolerated, and reported AEs related to the treatment were mostly classified as mild. A serious AE was reported by two participants in the snus group (pregnancy and vaginal bleeding during pregnancy), none of which was considered related to the allocated treatment compared with two participants in the placebo group. Five participants in the snus group experienced an AE that led to study discontinuation (sore gums, vaginal bleeding with pregnancy, glossitis and pharyngitis, diarrhea and dyspepsia, and pregnancy) compared with one participant in the placebo group (dysaesthesia).

Overall, 616 AEs were reported by 200 subjects, with 350 AEs reported in the snus group and 266 AEs in the placebo group (Table 4).

Treatment-related AEs more frequently reported in the snus group compared with the placebo group included gingival pain (19% vs. 13%), nausea (10% vs. 7%), dyspepsia (10% vs. 5%), gingivitis (3% vs. 1%), salivary hypersecretion (4% vs. 0%), dizziness (4% vs. 0%), hiccups (6% vs. 0%), and pharyngitis (5% vs. 2%).

Discussion

The observed overall smoking cessation success rates were generally low: Only five participants from the snus group (4%) were objectively verified as continuous abstainers from Weeks 6 to 28 compared with two (1.6%) in the placebo group corresponding to an odds ratio (OR) of 2.5 (95% CI: 0.4–27). There was no statistically significant evidence that the effect of snus on smoking cessation was different in subsets defined according to age, gender, previous quit attempts with NRT, or other baseline characteristics. Typically, cessation studies including participants motivated to quit report 6-month continuous abstinence rates of 20%–30% for active medication and 10%–15% for placebo. Although one of the inclusion criteria in this study was motivation to quit, current efficacy results are more comparable to those typically seen in smoking reduction trials, including smokers with no immediate wish to stop smoking completely. It is also possible that the negative cultural connotations of using smokeless tobacco in the United States, where smokeless tobacco is regarded as harmful as cigarette smoking (O’Connor et al., 2007), contributed to the observed low success rates. Future trials of snus to promote smoking cessation should probably use more stringent selection of participants and include more active counseling and psychosocial support.

Another circumstance that may have contributed to the observed generally low level of quitting was that, unlike most smoking cessation studies that included many visits to cessation...
experts in a special smoker's clinics, this study required only four clinical visits after baseline, and the centers had no previous experience with smoking cessation interventions. Many subjects were recruited from a database of research volunteers, whereas most prior trials recruited via referrals or public advertisements. Also, use of study products was relatively limited. Higher cessation rates with snus are reported in real-life surveys of Swedish and Norwegian smokers (Lund et al., 2011; Ramström & Foulds, 2006). This is likely due to self-selection of subjects and perhaps due to phasing in ST use over a much longer period. Also, the culture of using ST in Scandinavia may be different to the one in the United States. The wider accessibility of snus from price and number of purchase points of view speaks to a potentially good effectiveness.

Nevertheless, although not statistically significant, the OR for the snus versus placebo groups in the current study was similar compared with that reported for NR products (Stead et al., 2008). In addition, statistically significant differences favoring active snus occurred in several of the early outcomes. We believe these results suggest that snus has promise as a smoking cessation treatment and should be further evaluated under more optimal conditions.

No unexpected side effects were observed, but the amount of product used was also in most cases limited. Although the number of dropouts due to AEs was slightly higher in the snus group, the absolute rate of such dropouts was small (4%) and similar to that observed with other smoking cessation medications. The most common treatment-related AEs were similar to those observed with orally administered NRT (e.g., nausea, dyspepsia, hiccups). What was specific to this product was gingival pain most likely due to the product’s relatively high pH and the placement under the upper lip (Mills, Wu, Lockhart, Wilson, & Ebbert, 2010).

The major strength of this study is that it was a randomized placebo-controlled trial to test the smoking cessation efficacy of snus in a research design identical to that used for testing smoking cessation medicines. The study methods were similar to those for most clinical trials and were consistent with Society for Research on Nicotine and Tobacco guidelines (Hughes et al., 2003). As noted above, the major limitations were the lack of experience among study staff, the methods used for recruitment of participants, the clinical settings, and the relatively low use of study products.

In summary, although this study did not show a statistically significant increase in long-term prolonged abstinence, the positive short-term results and the lack of major AEs suggest that ST could be another tool in the armamentarium for stopping smoking. We believe that a test of snus in a more supervised clinical setting with more expertise and a greater sample size is indicated.

| Table 4. Incidence of AEs With Number of Participants Reporting in Parentheses |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Snus, n = 125   | Placebo, n = 125| Odds ratio (snus vs. placebo) | 95% CI         | p Value         |
| Any AE                           | 350 (99)        | 266 (101)       |                              |                 |                 |
| Mild                             | 274 (98)        | 217 (94)        |                              |                 |                 |
| Moderate                         | 53 (27)         | 34 (26)         |                              |                 |                 |
| Severe                           | 8 (6)           | 7 (5)           |                              |                 |                 |
| Unknown                          | 15 (7)          | 8 (8)           |                              |                 |                 |
| Possibly, probably, or definitely related AE | 149 (68)       | 91 (52)         |                              |                 |                 |
| AE leading to study discontinuation | 8 (5)          | 1 (1)           |                              |                 |                 |
| Serious AE                       | 2 (2)           | 3 (2)           |                              |                 |                 |

Note. AE = adverse event.

<table>
<thead>
<tr>
<th>Table 3. Biologically Verified Smoking Cessation Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Continuous cessation</td>
</tr>
<tr>
<td>Weeks 6–16</td>
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<tr>
<td>Weeks 6–28</td>
</tr>
<tr>
<td>Point prevalence cessation</td>
</tr>
<tr>
<td>Week 6</td>
</tr>
<tr>
<td>Week 16</td>
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<tr>
<td>Week 28</td>
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</tbody>
</table>

Snus as a smoking cessation aid
Authors’ Contributions

KF was responsible for the design of the study, drafted the study protocol, participated in the statistical analyses, and drafted the manuscript. JRH participated in the design of the trial and helped to draft the manuscript. LER participated in the trial design, was responsible for study product logistics, and helped to draft the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

Acknowledgments

We are indebted to the following principal investigators: Dr. Frank Farmer Jr. (Covance Clinical Research, Inc., Daytona Beach, FL), Dr. David C. Carter (Covance Clinical Research, Inc., Austin, TX), Dr. Keith Klatte (Covance Clinical Research, Inc., Portland, OR), Dr. Randall Stoltz (Covance Clinical Research, Inc., Evansville, IN), and Dr. Georgia Latham (Covance Clinical Research, Inc., Dallas, TX).

References


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