



RJ Reynold's Unpublished Randomized Controlled Trial Finds that Camel Snus is Not Effective for Smoking Cessation

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RJ Reynold's Unpublished Randomized Controlled Trial Finds that Camel Snus is Not Effective for Smoking Cessation

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RJ Reynolds' Unpublished Study on Camel Snus Compared to Nicotine Replacement Therapy for Smoking Cessation is Responsive to FDA's Request for Studies Regarding Predictors of Consumer Initiation, Uptake, and Use of a Tobacco Product

FDA's Request for Information on Psychosocial Predictors of Uptake of Tobacco and Other Products (RFI) specifies that FDA is seeking unpublished data and information that could help identify and evaluate predictors of consumer initiation, uptake, and use of tobacco products. Between 2009-2014, RJ Reynolds (RJR), created, conducted, and presented to a tobacco industry trade group, CORESTA Congress, a randomized control trial that compared Camel Snus to Nicorette nicotine replacement therapy (NRT) for smoking cessation over one year. As described below, we were able to find some data and information in the Truth Tobacco Industry Documents about RJR's randomized controlled trial which shows that Camel Snus is not effective for long term smoking cessation.

RJ Reynolds Conducted, but Did Not Publish, a Well-Done Negative Randomized Controlled Trial of Camel Snus compared to NRT for Smoking Cessation

In 2009, RJR created "The Smoker Cessation/Migration Study/CSD0909/CSD1010" a randomized control trial, to **compare Camel Snus to Nicorette nicotine replacement therapy (NRT) for smoking cessation over one year.**[1] The RJR randomized controlled trial also examined the effect of providing information on the health benefits of switching from cigarettes to smokeless tobacco products (STP) on smoking cessation. RJR's clinical studies division,[2] together with legal, financial, marketing, and innovation teams,[3] designed the protocol. The study had three arms, with **200 smokers in each: 1) Camel Snus** with subjects being told at the beginning of the study that Camel Snus had **lower health risks** than cigarettes; 2) **Camel Snus without any health risk information**; and 3) **Nicorette lozenges**. All participants were **given study products for 12 weeks to aid with smoking cessation.**[4] Biochemically-verified cigarette smoking status (exhaled CO and cotinine levels) was recorded at baseline and at 3, 6 and 12 months to determine point prevalence and continuous abstinence.[5] The study was powered to detect an absolute **10% difference in smoking cessation.**[6] RJR considered comparing Camel Snus to quitting "cold turkey," but RJR did not undertake such a study due to concerns that the study would show that Camel Snus was not superior to cold turkey.[7] Recruitment occurred in 2011-2012[8] and data collection appears to have been completed in 2013.

Abstracts reporting the study's design and some of the results were presented at the October 2014 CORESTA Congress, an international tobacco industry trade association, and were found in the UCSF Truth Tobacco Documents Library.[9] The results showed that **smoking cessation rates were low, 1-5% depending on the endpoint**, and were statistically insignificant among the three arms. Participants, who continued smoking and used study products, reduced their cigarette consumption, ($p < 0.05$) although the amount was not reported.

Despite being a well-designed study, we found no evidence that RJR's protocol was registered at ClinicalTrials.gov. We also searched PubMed.gov and scholar.google.com and did not find any evidence that the results were published in the open scientific literature.

The demonstration that Camel Snus with or without education on the purported lower health risk of smokeless tobacco was no better than unsupervised NRT at promoting smoking suggests that Camel Snus is actually depressing quitting because over-the-counter NRT effectiveness is associated with significantly lower odds of abstinence compared to smokers using no cessation aids to quit.[10]

The Unpublished RJR Randomized Controlled Trial Found Results Consistent with a Similar Study Done by Dorothy Hatsukami

Before the study was designed, RJR was aware of a similar study planned by University of Minnesota professor Dorothy Hatsukami because Hatsukami contacted RJR in 2006 to purchase Camel Snus for her study.[11] Hatsukami's study compared Camel Snus, Taboka (a snus product from Philip Morris), and nicotine gum for 16 weeks to determine how smokers interested in cessation used these products.[12] Hatsukami also measured differences in tobacco specific nitrosamines (TSNAs) and cotinine levels among product groups, and the products' cessation feasibility. This pilot study collected smoking status for preliminary data, but was not powered to detect cessation differences.[13]

In 2010-2014, Hatsukami subsequently recruited and completed a study that had 80% power to detect a 10% difference in smoking cessation that, like the RJR study, found no significant difference in continuous smoking cessation at 26 weeks between Camel Snus and nicotine gum users randomized to use these products for 12 weeks (2.6% vs 5.1%, respectively).[14]

Hatsukami also reported that Camel Snus users had greater toxicant (TSNA) exposure and less satisfaction than nicotine gum.[15] RJR, unlike Hatsukami, did not measure any biomarkers of harm in its study.

RJR's Study Comparing Camel Snus to NRT Provides FDA with Valuable Information Concerning Psychosocial Predictors of Effective – and Ineffective – Products and Techniques for Cessation

RJR's research is helpful to FDA because, combined with the Hatsukami study, it shows that two separate RCTs demonstrate that Camel Snus does not sustain smoking cessation. Both the unpublished RJR RCT and Hatsukami's RCT showed low (<~5%) long term smoking cessation rates among smokers who used Camel Snus to quit smoking.

Pursuant to Section 904(b), FDA Should Order RJR to Submit Any or All Documents, Including Underlying Scientific Information, Raw Data, All Versions of Research Protocols, All Analyses, and All Reports, Both Published and Unpublished, That RJR Conducted, Supported, or Possessed Concerning Its Randomized Control Trials of Camel Snus for Smoking Cessation, Including but not Limited to Comparison to Nicotine Replacement Therapies

While the publicly available documents in the Truth Initiative Tobacco Documents Library describe the RJR randomized controlled trial and its results, there are an additional 29 related documents developed after June 22, 2009 that RJR has not made public (Table 1).

Section 904(a)(4) of the Family Smoking Prevention and Tobacco Control Act[16] (TCA) created an ongoing requirement beginning December 22, 2009 for each tobacco product manufacturer or importer or their agent to submit to FDA all documents developed after June 22, 2009 "that related to health, toxicological, behavioral, or physiologic effects of current or future tobacco products, their constituents (including smoke constituents), ingredients components, and additives." FDA published a Guidance for Industry on Tobacco Health Document Submission (Guidance) in April 2010 that provides details about what information, documents, and metadata is required to be included in industry submissions.[17] The Guidance emphasizes that failure to provide any information required by section 904 is a prohibited act under TCA section 301(q)(1)(B), and renders the tobacco product misbranded under section 903(a)(1). Further, the Guidance states that violations relating to section 904(a)(4) are subject to regulatory and enforcement action by FDA, including seizure and injunction. TCA section 303(f)(9) provides for civil monetary penalties for violation of tobacco product requirements, including an enhanced penalty of up to \$250,000 per violation for intentional violations of section 904 requirements.[18]

In addition to the ongoing requirement described in section 904(a), section 904(b) provides that at the request of FDA, tobacco product manufacturers must submit "(1) any or all documents (including underlying scientific information) relating to research activities, and research findings, conducted, supported or possessed by the manufacturer (or agents thereof) on the health, toxicological, behavioral, or physiologic effects of tobacco products...;" "(2) any or all documents (including underlying scientific information) relating to research activities, and research findings, conducted, supported or possessed by the manufacturer (or agents thereof) that relate to the issue of whether a reduction in risk to health from tobacco products can occur upon the employment of technology available or known to the manufacturer...;" and "(3) any or all documents (including underlying financial information) relating to marketing research involving the use of tobacco products or marketing practices and the effectiveness of such practices used by tobacco manufacturers and distributors." [19]

RJR's unpublished randomized control trial comparing the effectiveness of Camel Snus to Nicorette nicotine replacement therapy (NRT) for smoking cessation is an example of a document developed after June 22, 2009 that relates to the marketing as well as to the health, behavioral, and/or physiologic effects of Camel Snus, a smokeless tobacco product marketed by RJR and subject to TCA section 904. RJR's study found that using Camel Snus (with or without education on the lower risk of smokeless tobacco compared to cigarettes) was no better than NRT at promoting smoking cessation.

Any research conducted or supported by RJR on the effectiveness of snus for cessation and/or harm reduction would be tobacco health documents required to be submitted to FDA under section 904(a) and valuable to FDA to evaluate whether Camel snus would be effective for cessation and/or harm reduction.

Whether or not RJR submitted a health report that summarized one or more trials, FDA has the authority under section 904(b) to request and require RJR to submit any or all documents concerning these research activities, including all raw data collected and any and all analyses conducted, supported, or possessed by RJR, as well as all versions of the research protocol(s) used. The documents we uncovered in the Truth Tobacco Industry Documents suggest one of the earliest protocols by Paul Nelson, from the clinical studies division,[20] may have changed.

Table 1. Additional Confidential RJR Documents in the Truth Tobacco Industry Documents That FDA Should Obtain to Better Understand RJR's Study Comparing Camel Snus to NRT Effect on Cigarette Consumption, Role in Smoking Cessation, and Camel Snus Uptake (available in PDF)

[1] Nelson P. Smoker Cessation Migration Study - Draft. May 29, 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/gtjm0222> (accessed 2015 December 28); RJR Product Integrity Group. Smoking Cessation Migration Study. June 05, 2009. <https://idl.ucsf.edu/tobacco/docs/ksjm0222> (accessed 2016 January 03); Interview Ethical Review Board. Informed Consent Document Agreement To Be In A Research Study. CSD1010; "A Randomized, Multicenter Clinical Trial To Compare Smoking Cessation Rates With Camel Snus, With And Without Smokeless Tobacco Health-Related Background Information, And A Nicotine Lozenge". February 11, 2011. <https://industrydocuments.library.ucsf.edu/tobacco/docs/#id=fxlv0190> (accessed 2016 February 20)

[2] Nelson P. Smoker Migration Synopsis - Current Draft. May 21, 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/htjm0222> (accessed 2015 December 28)

[3] Mitchell P. Agenda and Pre-Reads for Tuesday R&D Leadership Team Meeting. June 5, 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/ypfm0222> (accessed 2015 December 28)

- [4] Nelson P, Chen P. Clinical Trial to Compare Smoking Cessation Rates with Camel Snus and a Nicotine Lozenge (Coresta Congress , Quebec , 2014 , Smoke Science/Product Technology Groups , Abstracts ST81, ST82) 2014. <https://idl.ucsf.edu/tobacco/docs/hqmx0223> (page 40) (accessed 2015 December 28)
- [5] RJR Product Integrity Group. Smoking Cessation Migration Study. June 05, 2009. <https://idl.ucsf.edu/tobacco/docs/ksjm0222> (accessed 2016 January 03); Nelson P, Chen P. Clinical Trial to Compare Smoking Cessation Rates with Camel Snus and a Nicotine Lozenge (Coresta Congress , Quebec , 2014 , Smoke Science/Product Technology Groups , Abstracts ST81, ST82) 2014. <https://idl.ucsf.edu/tobacco/docs/hqmx0223> (page 40) (accessed 2015 December 28);
- [6] RJR Product Integrity Group. Smoking Cessation Migration Study. June 05, 2009. <https://idl.ucsf.edu/tobacco/docs/ksjm0222> (accessed 2016 January 03)
- [7] Nelson P. Smoker Cessation Migration Study - Draft. May 29. 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/gtjm0222> (accessed 2015 December 28)
- [8] Central Kentucky Research Associates. Protocol: RJR - Smoking Cessation - #CSD1010. March 15, 2011. RJ Reynolds. <https://idl.ucsf.edu/tobacco/docs/yxlv0190> (accessed 2015 December 28); Central Kentucky Research Associates. Stop Smoking. <https://www.facebook.com/CKRAResearch/?fref=ts> (accessed 2016 February 20); Columbia Research Group. Columbia Research Group Is Looking For: Smokers Ready to Quit. February 09. 2011. RJ Reynolds. <https://idl.ucsf.edu/tobacco/docs/lxlv0190> (accessed 2015 December 28); Comprehensive Neuroscience, Reynolds American, Metaclin Research, et al. RJR Protocol_CSD1010_ Revised Ads_Site 005 January 10, 2011. RJ Reynolds. <https://idl.ucsf.edu/tobacco/docs/nsmc0190> (accessed 2015 December 28); Nelson V, Orlando Clinical Research Center. Request for Review of Recruiting/Miscellaneous Materials Form. Protocol No.: CSD1010. Want to Quit Smoking. March 25, 2011. RJ Reynolds. <https://idl.ucsf.edu/tobacco/docs/gxlv0190> (accessed 2015 December 28)
- [9] Nelson P, Chen P. Clinical Trial to Compare Smoking Cessation Rates with Camel Snus and a Nicotine Lozenge (Coresta Congress , Quebec , 2014 , Smoke Science/Product Technology Groups , Abstracts ST81, ST82) 2014. <https://idl.ucsf.edu/tobacco/docs/hqmx0223> (page 40) (accessed 2015 December 28)
- [10] Kotz D, Brown J, West R. Prospective Cohort Study of the Effectiveness of Smoking Cessation Treatments Used in the "Real World". Mayo Clin Proc 2014;89:1360-7.
- [11] Hatsukami D, Cook C. Camel Snus. October 2, 2006. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/xjnf0222> (accessed 2015 December 28)
- [12] Tobacco Use Research Center, University of Minnesota. Comparing the Health Effects of Smokeless Tobacco, Cigarette Smoking, and New Tobacco Products Advertised as Safer Alternatives. November 06. 2006. RJ Reynolds. <https://idl.ucsf.edu/tobacco/docs/mnbl0222> (accessed 2016 January 04); Hatsukami D. ClinicalTrials.gov, Health Effects of SLT, Cigarette Smoking, and New Tobacco Products (Ants3). May 3, 2007. <https://clinicaltrials.gov/ct2/show/study/NCT00469079?term=camel+snus+ta...> (accessed January 4, 2016); Kotlyar M, Hertsgaard LA, Lindgren BR, et al. Effect of Oral Snus and Medicinal Nicotine in Smokers on Toxicant Exposure and Withdrawal Symptoms: A Feasibility Study. Cancer Epidemiol Biomarkers Prev 2011;20:91-100.
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- [14] Hatsukami DK, Severson H, Anderson A, et al. Randomised Clinical Trial of Snus Versus Medicinal Nicotine among Smokers Interested in Product Switching. Tob Control 2015:Epub ahead of print May 2015
- [15] Hatsukami DK, Severson H, Anderson A, et al. Randomised Clinical Trial of Snus Versus Medicinal Nicotine among Smokers Interested in Product Switching. Tob Control 2015:Epub ahead of print May 2015
- [16] Family Smoking Prevention and Tobacco Control Act, Public Law 111-31, 21 U.S.C. 387d(a)(4), June 22, 2009.
- [17] Food and Drug Administration, Center for Tobacco Products, Guidance for Industry – Tobacco Health Document Submission, OMB control number: 0910-0654, April 2010. <http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM208916.pdf>
- [18] Family Smoking Prevention and Tobacco Control Act, Public Law 111-31, 21 U.S.C. 333(f)(9)(B)(i), June 22, 2009.
- [19] Family Smoking Prevention and Tobacco Control Act, Public Law 111-31, 21 U.S.C. 387d(b), June 22, 2009
- [20] Nelson P. Smoker Cessation Migration Study-Draft. May 29. 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/gtjm0222> (accessed 2015 December 28); Nelson P. Smoker Migration Synopsis - Current Draft. May 21. 2009. RJ Reynolds. <https://industrydocuments.library.ucsf.edu/tobacco/docs/htjm0222> (accessed 2015 December 28)

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