Review of: "A Randomised, Crossover, Clinical Study to Assess Nicotine Pharmacokinetics and Subjective Effects of the BIDI® Stick ENDS Compared with Combustible Cigarettes and a Comparator ENDS in Adult Smokers"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

General Comment

The manuscript reports results of a randomised, crossover, clinical study to assess nicotine pharmacokinetics and subjective effects of the BIDI® Stick ENDS compared with subjects' usual brand (UB) combustible cigarettes and a comparator ENDS (JUUL) in adult smokers. The primary findings were that nicotine delivery and subjective effects from the investigational product (BIDI) was match the subjects UB combustible cigarettes.

The data provided in the manuscript addresses the role ENDS offer in switching smokers of combustible cigarettes to less harmful alternatives. For successful switching, the authors make a case for nicotine delivery and product satisfaction as critical to sustained smoking cessation using data generated from the study.

While the paper provides some strong argument, there are several elements of the study design which could be clarified in the manuscript. For example, the introduction has not discussed some of the critical elements of the study such as the effect of nicotine salts, sensory, and flavours, but rather focuses solely on nicotine delivery as the drive for ENDS acceptance. Furthermore, the methodology could be strengthened by providing additional details about the rationale for the study design. For example, why the cigarette arm assessment was carried out first and not randomised as this could potentially create bias. Lastly, the discussion section attempts to draw inference to nicotine dependency, when clearly the current study design is not an abuse liability study, rather, it a safety and efficacy study.

Several questions and comments are listed below.

Abstract:

1. Please state the total duration of the defined puff session.

Introduction

1. By definition, a disease is a pathophysiological response to internal or external factors. A disorder is a disruption to regular bodily structure and function. While smoking can cause structural and functional disruption down the line, the examples you have provided are diseases not disorders. I suggest replacing disorder with disease in line 3 of paragraph 1.
2. Provide reference to the data that shows that large number of adults smokers desire of stop smoking in line 8 of paragraph 1.
3. It is unclear how the Russel 1976 paper referenced is appropriate for the statement proposing an alternative forms of nicotine delivery. Russel did not propose an alternative nicotine delivery system e.g., e-cigarette. What the paper proposed is a low tar cigarette, which in the real sense is still a cigarette. Could you please provide relevant reference to the first sentence in paragraph 2?
4. In the second paragraph, the manuscript states that “exposure to cigarette smoke toxicants is either greatly reduced or absent in smokers who completely switch to ENDS”. Greatly reduced, yes, but absent is a stretch. None of the BoE or BoPH studies cited had complete elimination of harmful toxicants. However, there is no epidemiological studies yet, so it is better to be careful when making this statement. The current best estimate by PHE is that using EC is around 95% safer than smoking – the 5% here is still a risk. Please revise the sentence.
5. Second sentence in 3rd paragraph is lengthy which does not pass across the message in a coherent manner. Please revise.
6. 3rd paragraph emphasises nicotine delivery as key to ENDS acceptance but fails to acknowledge other factors such as sensory, flavours etc. In addition, since the study has nicotine salts, it is worth discussing the role this plays in the introduction.

Methods

1. What is the rationale for having the cigarette PK session first before ENDS products? Please discuss.
2. Since the BIDI products are disposable, how was familiarisation ensured? Please explain this in the methods section.
3. In the Nicotine Pharmacokinetics section, please state the total duration of each use session.
4. The additional 60 minutes product use at the end of the defined product use – please could you discuss the rationale for this? What information or value did this add to the study design?
5. Was ENDS product use measured? For example, puff count during the ad libitum session. Also, Device Mass Loss (for e-liquids) and Mouth Level Exposure (for cigarettes) also offers useful information on use behaviour? If these were not collected, then I believe this should be captured as a limitation to the study.
6. Is the protocol provided as part of the supplementary information? This would be helpful

Results

1. So that the manuscript can be easily followed, please be consistent with your use of “controlled session” or “defined session”.

Discussion

1. First Paragraph focuses on nicotine delivery as a key to sustained switching to ENDS; however, fails to acknowledge other factors. Please discuss other factors.
2. Paragraph attempts to link this simple safety and efficacy PK study to dependency i.e. abuse liability. The study design is not an abuse liability study and it not powered for this. Any inference on abuse liability is conjecture. I suggest this paragraph and the next should be re-written or deleted.
3. In the limitations, line 9 should be study (singular), not studies. Also, it is worth capturing that product use was not assessed to determine variations in subjective behaviour.