

# Evaluation of Biomarkers of Exposure and Cardiovascular & Pulmonary Function Endpoints in Adult Smokers Following Partial or Complete Substitution of Cigarettes with Electronic Cigarettes



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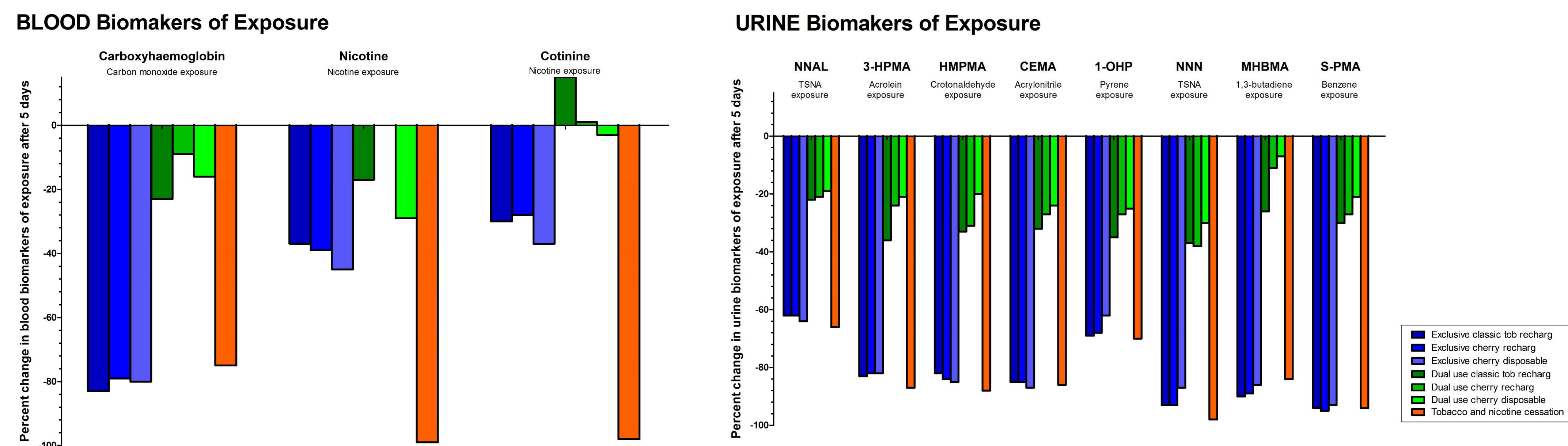
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## 1. Introduction and Study Overview

- E-cigarettes are becoming an increasingly popular alternative to conventional tobacco cigarettes among smokers worldwide.
- The concentration of toxicants in e-cigarette aerosols are reportedly tens to thousands times lower than in tobacco smoke [1]; many toxicants are simply not present in e-cigarette aerosols at detectable levels including constituents in tobacco smoke categorised by the FDA as being harmful and potentially harmful constituents (HPHCs). To date, there is relatively little information available on consumer exposure to HPHCs resulting from the use of e-cigarettes compared to conventional cigarettes.
- The primary objective of this study was to compare changes in selected urine, blood and exhaled breath biomarkers of exposure to HPHCs, which according to FDA are representative of the most significant contributors to smoking-associated disease risks, and to nicotine. Different user groups each followed a 5 day forced-switch from their usual conventional cigarette brand to either: (i) exclusive use of a commercially available blu™ e-cigarettes; (ii) dual use of a commercially available blu™ e-cigarettes and usual conventional cigarette brand; or (iii) discontinued use of all tobacco or nicotine products.
- The secondary objectives of this study were to assess: (i) the short-term changes in selected cardiovascular (systolic and diastolic blood pressure and heart rate) and pulmonary function (FVC, FEV1) endpoints; (ii) the effectiveness of e-cigarettes to reduce the desire to smoke and (iii) the potential safety and adverse events associated with use of the products.
- Clinically-confined smokers ( $n=105$ ) were randomized into groups that partially or completely substituted their usual conventional cigarette brand with commercially available cherry disposable, classic tobacco or cherry rechargeable closed system blu™ e-cigarettes (2.4% nicotine), or discontinued all tobacco or nicotine products for 5 days. Dual users could smoke no more than 50% of the number of cigarettes per day reported during screening (hence 'partial substitution'). Subjects were familiarised with the e-cigarette device during enrolment. Products were used *ad libitum* throughout and the study was conducted in the USA. Method details [2].

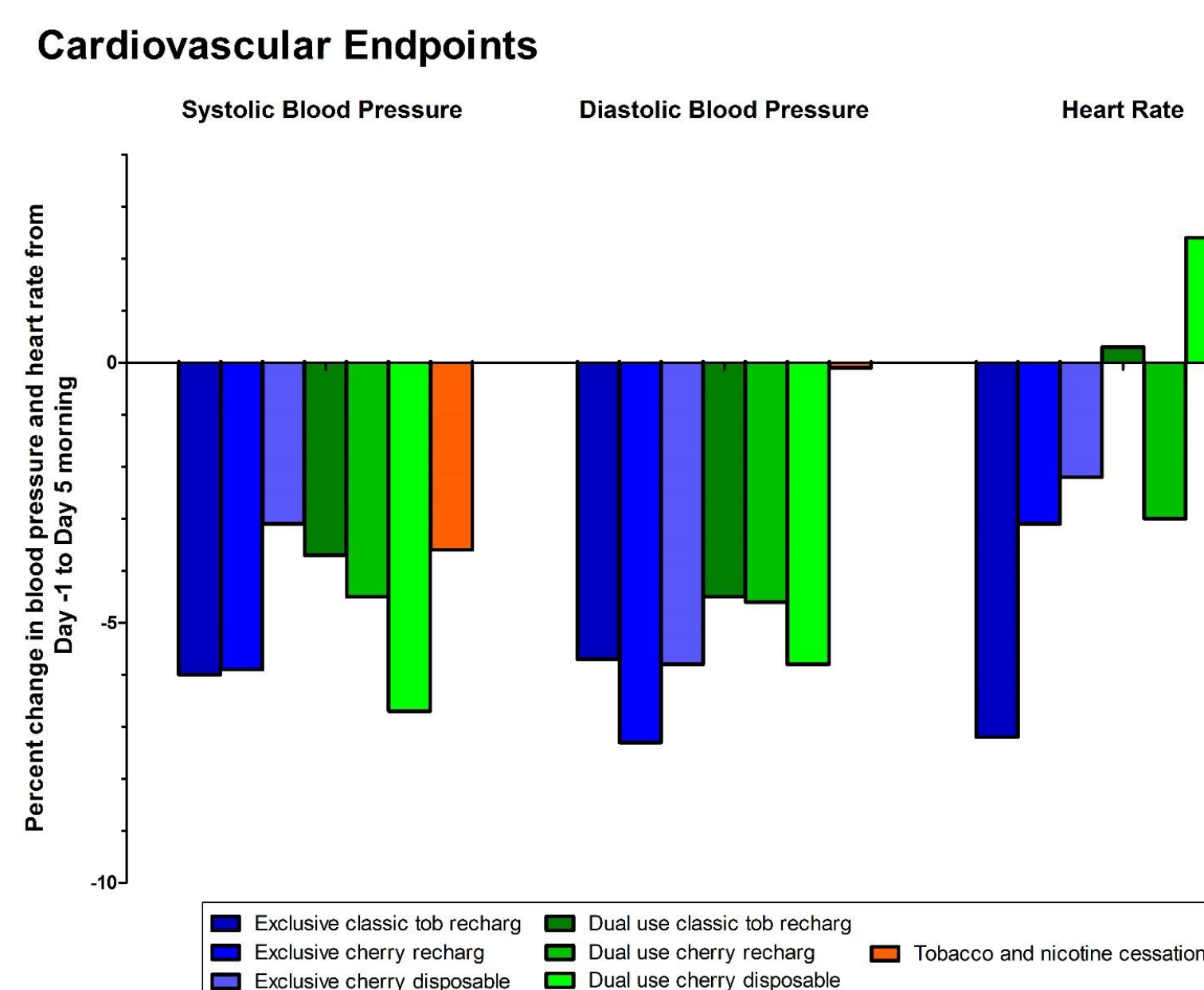
## 2. Reductions in Blood and Urine Biomarkers of Exposure to Nicotine and HPHCs from Day -1 (Baseline) to Day 5



- Reducing consumption of conventional cigarettes over 5 days according to the requirements of the study resulted in sizeable reductions in exposure to selected HPHCs and nicotine.
- Smoking cessation lead to a 66% to 98% reduction in excretion of the urine biomarkers of exposure evaluated in this study. The smallest reduction was observed for NNAL, which has the longest half-life of the individual biomarkers listed. Predictably, significant decreases were also observed in COHb, nicotine, and the nicotine metabolite cotinine, as the cessation subjects had no exposure to CO or nicotine.
- The reductions in biomarkers of exposure to HPHCs observed in the exclusive e-cigarette use group (62% to 95%) were mostly comparable to those observed in the cessation group. There were notable exceptions for nicotine and the nicotine metabolite biomarker as these subjects continued to consume nicotine from the e-cigarettes.
- Over the course of the study, dual users smoked 52% fewer conventional cigarettes compared to screening and 33% fewer compared to Day -1 (baseline). Dual users who had substituted half of their self-reported daily cigarette consumption with e-cigarettes exhibited reduced biomarker levels that appear broadly proportional to the reduced numbers of cigarettes smoked. Reductions in the urine biomarkers of exposure for this group ranged from 7% to 38%. The nicotine metabolite cotinine was an exception, with a reported non-statistically significant increase in blood at the end of the exposure study.

## 4. Changes in Blood Pressure and Heart Rate Endpoints

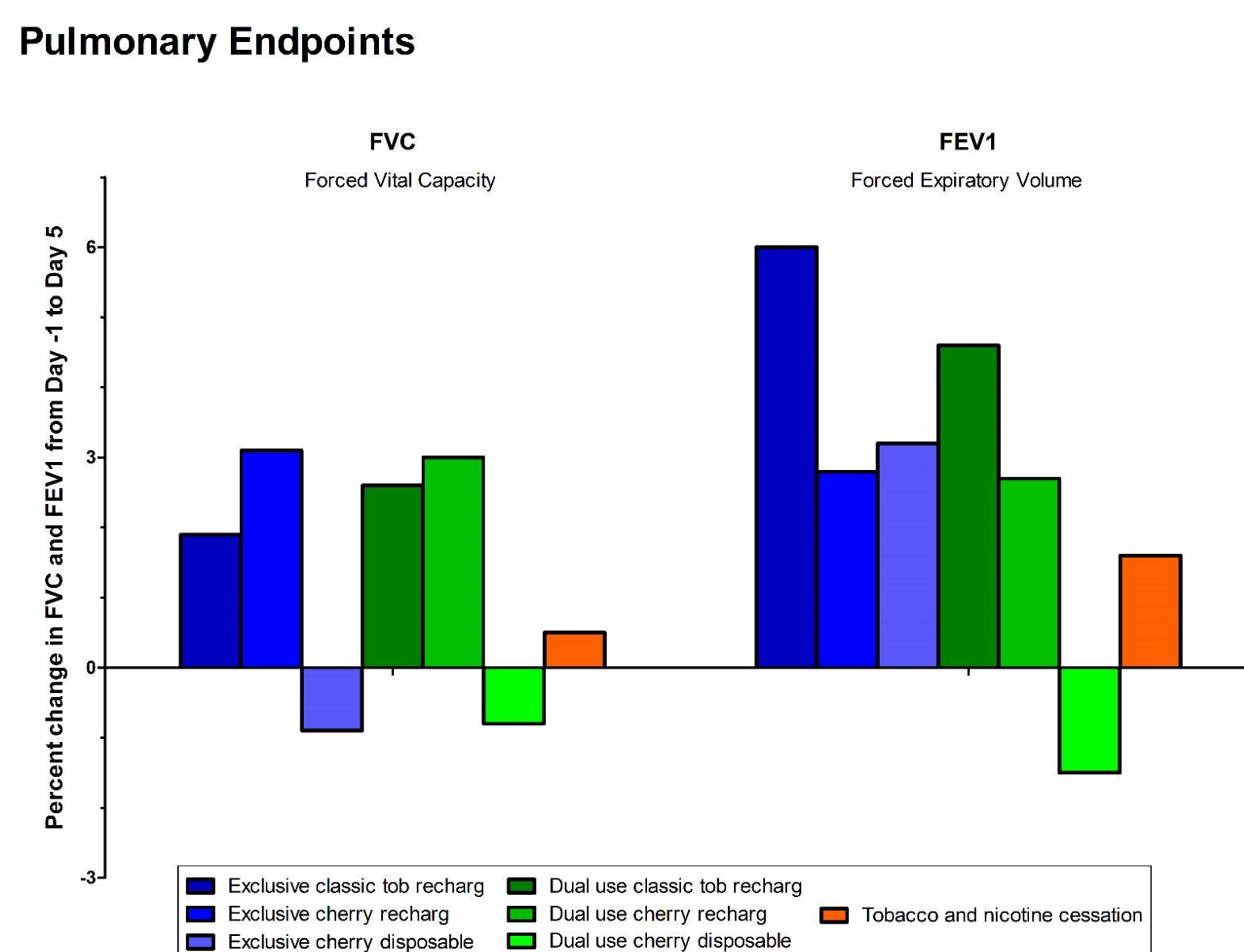
- Smoking is a cause of serious diseases in smokers including heart disease [3]. Increased blood pressure and heart rate have been associated with heart disease.



- All groups experienced reductions in both systolic and diastolic blood pressure at Day 5 vs. Day -1 (baseline). Similarly, all groups experienced reductions in heart rate at Day 5 vs. Day -1, except for the dual users of the classic tobacco rechargeable and cherry disposable products which showed a slight increase.

## 5. Changes in FVC and FEV1 Pulmonary Endpoints

- Smoking is a cause of serious diseases in smokers including lung cancer [4]. Pulmonary function can be measured by forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) parameters as they provide an indication of airway obstruction.

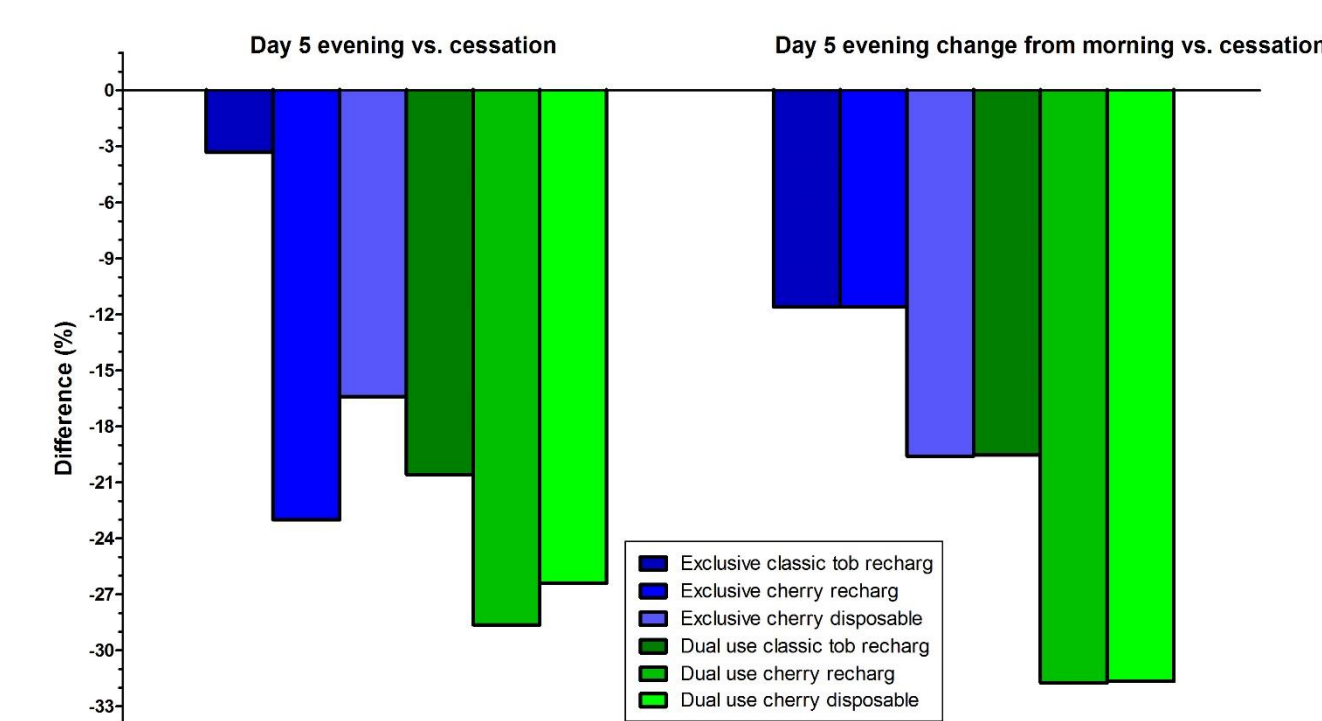


- Following a 5 day forced-switch, small improvements in FVC ranging from 0.5% to 3.1% were observed in all user groups except for the exclusive cherry disposable and cherry rechargeable dual users. Similarly, improvements in FEV1 values, ranging from 1.6% to 6% were also observed in all use groups except for the cherry rechargeable dual users, which experienced a small decrease of -1.5%.
- Pulmonary improvements were also noted in exhaled CO and NO endpoints (Section 3).

## 6. Reduction in Desire to Smoke and Product Safety

### DESIRE TO SMOKE A CONVENTIONAL CIGARETTE

- Desire to smoke a conventional tobacco cigarette was assessed on Days -1 through 5 in the morning prior to the start of product use and in the evening via use of a subjective visual analogue scale. Subjects were asked to rate "how strong is your urge to smoke right now?" by placing a cross through a 100 mm line where far left indicated: 'not at all' and far right indicated: 'extremely'.

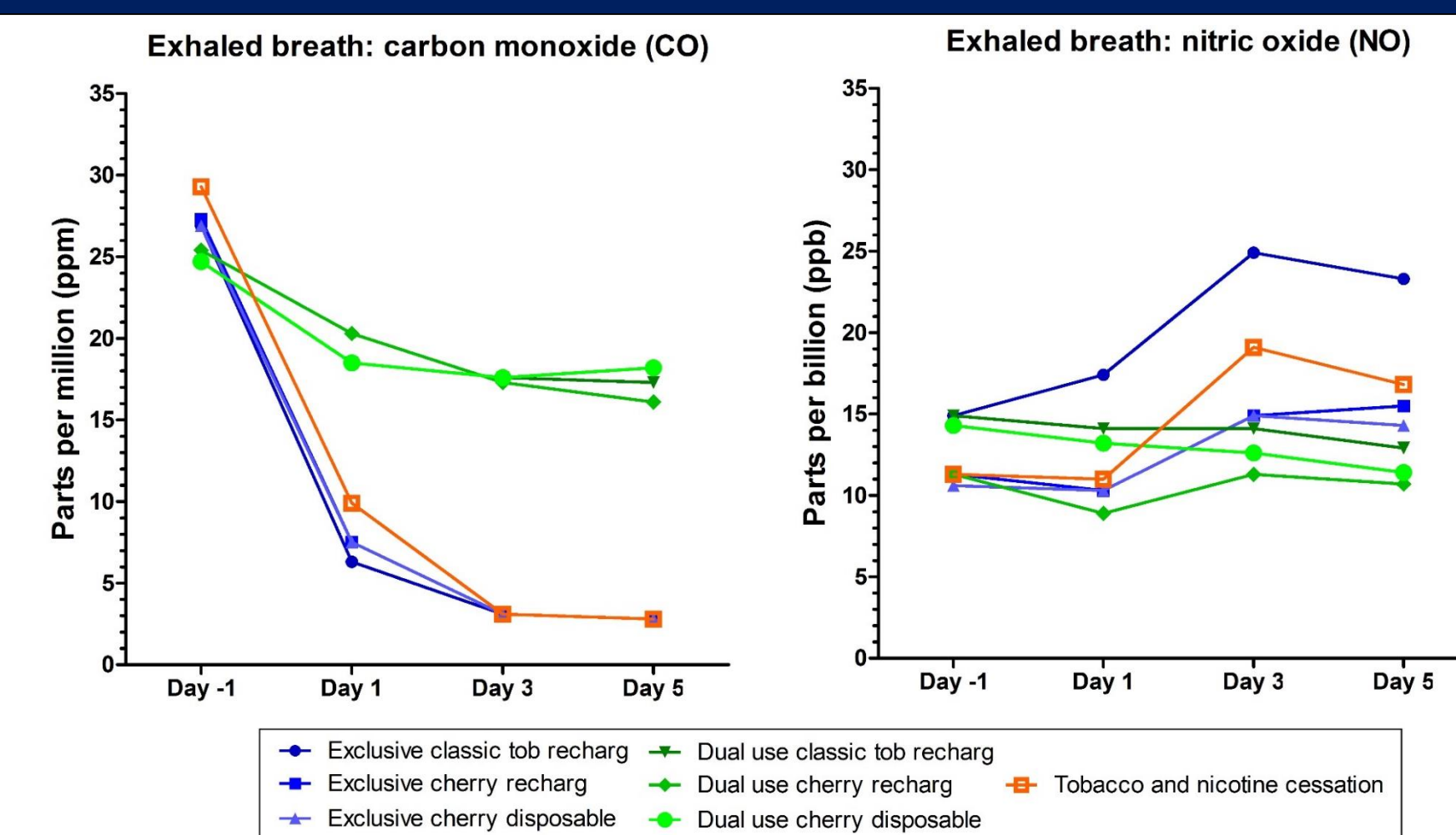


- By Day 5, both exclusive and dual use groups had greater reductions in smoking desire compared to cessation. Reductions were larger in the dual use group.

### TOLERABILITY AND ADVERSE EVENTS (AEs)

- AEs reported by the subjects or observed by the clinic staff were assessed for severity (mild, moderate, or severe), as serious or not serious, and relationship to the study products by the Principal Investigator.
- Overall, 72 mild product-use AEs were experienced by 30% of subjects. The most frequently reported AE was headache across study groups; a common AE previously reported for nicotine replacement therapies [5].
- AEs were not deemed to be serious and no subjects were withdrawn due to AEs.

## 3. Changes in Exhaled CO and NO Levels



- Physiological changes associated with smoking reduction were noted in both exhaled carbon monoxide (CO) and nitric oxide (NO) endpoints.
- All groups experienced decreases in exhaled CO at Day 5 vs. Day -1 (baseline), with decreases in the cessation and exclusive e-cigarette use groups around 90%, and 31% in the dual use group. There were no differences between the cessation and exclusive use group measurements on Day 5 whereas the dual use group had higher exhaled CO compared to cessation. This was expected since this group still consumed conventional cigarettes.
- Smoking has been reported to decrease NO production, possibly by the inhibition of NO synthase, but the mechanism remains incompletely understood. Exhaled NO was observed to increase from Day -1 to Day 5 in the cessation (49%) and exclusive e-cigarette use groups (56%), whereas the dual use groups experienced minimal changes.

## 7. Conclusions

- The data presented here demonstrate that smokers who completely substituted conventional cigarettes with e-cigarettes over a short period of time (5 days) experienced reductions in exposure to a number of HPHCs and nicotine as measured by urine, blood and exhaled breath biomarkers of exposure (Section 2 and 3). The data show that subjects who switched to dual use also experienced reduced HPHC exposures after partially replacing cigarettes with the e-cigarette products, albeit to a lesser extent (Section 2 and 3).
- The cardiovascular data adds to the evidence that quitting smoking or reducing the number of cigarettes smoked with the use of e-cigarettes does not lead to higher blood pressure values (Section 4).
- The pulmonary data do not appear to support negative respiratory outcomes in users following short-term use of the e-cigarette products (Section 5). Whether flavourings pose any appreciable negative impact on pulmonary function from long-term use warrants further investigation.
- The e-cigarette products reduced the desire to smoke a conventional cigarette with greater reductions compared to the cessation group. Unlike conventional nicotine replacement therapies, e-cigarettes replicate the behavioural and sensorial aspects of smoking (Section 6).
- The e-cigarette products used in this study were well tolerated and no serious adverse events were reported under the experimental conditions (Section 6).
- Longer-term biomarker of effect studies investigating inflammatory and oxidative stress endpoints may be informative for assessing the long-term implications and physiological relevance of reduced exposure to HPHCs. This work is currently underway. Information from longer-term e-cigarette product tolerability and adverse event surveillance studies may also be informative.
- Overall, the present study shows the great potential that the blu™ closed system e-cigarettes may provide smokers seeking an alternative to conventional tobacco products.

## References

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