Control measures for assessing compliance in long-term Potentially Reduced Risk Product switching studies

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Introduction

Recently, clinical studies have shown reductions in exposure to tobacco smoke toxicants when smokers of conventional cigarettes switch to tobacco heating products (THP). These are generally short-term confined studies where compliance is well controlled. However, to investigate whether these reductions in exposure to cigarette toxicants can translate to reductions in smoking-related health risks, long-term studies are required. In this case, ambulatory studies are often the preferred approach, with subjects visiting the clinic at specific timepoints. Therefore, the potential for non-compliance, where the subject smokes conventional cigarettes and not the assigned THP, is high.

To address this, in a 12-month study examining health effect indicators when smokers switch to using the glo THP in the UK (ISRCTN81075760), we have incorporated a biomarker of compliance (BoC), the haemoglobin adduct of acrylonitrile, N-(2-cyanoethyl)valine (CEVal). This paper presents the results of a planned interim analysis of CEVal after 90 days.

Aim

To demonstrate the utility of CEVal as a biomarker for monitoring compliance in the 12-month study examining health effect indicators in the glo THP and nicotine cessation arms

Background

A schematic for the 12-month study is shown in Figure 1. This is an ambulatory study where subjects will go about their business as normal between study visits. Measures have been placed in the study to try to monitor compliance generally using subject diaries to record combustible cigarette usage in the glo THP switching and the nicotine cessation arms. As an additional measure, CEVal was analysed in blood samples taken at the clinic visits.

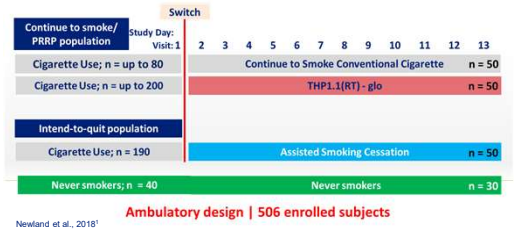

Figure 1: Schematic diagram of the study design

BoC have been used as a control measure in other clinical studies. Noad et al.[2] used plasma vitamin C and carotenoids as BoCs in subjects on a high-polyphenol diet via consumption of fruit and vegetables in their study investigating diet and hypertension. In another study reported by Harrison et al.[3] investigating dietary docosahexaenoic acid (DHA, long-chain omega 3) and soya protein effects on cholesterol and blood pressure. Compliance was also monitored using plasma DHA and urinary isoflavones.
The rationale for CEVal selection is described in Figure 2 and Figure 3.

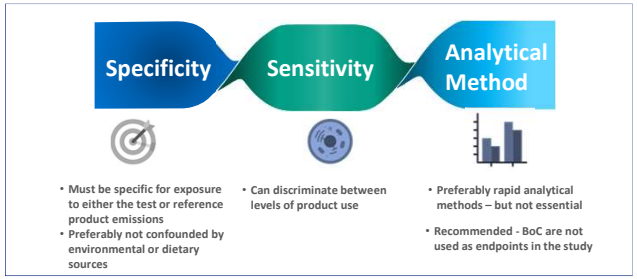

Figure 2: Requirements for BoC in a tobacco context

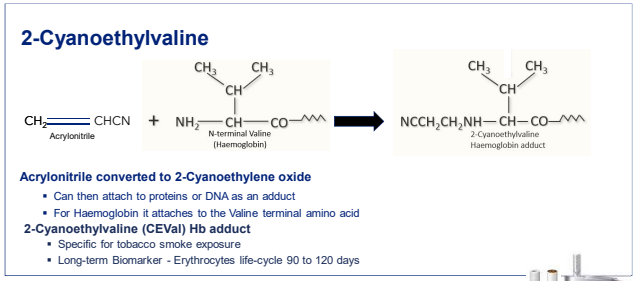

Figure 3: Formation of CEVal Hb adducts

Study Products

- Subjects' usual-brand cigarette
- glo THP (3.9 mg) nicotine tobacco sticks (Figure 4)

Figure 4: The glo tobacco heating product.

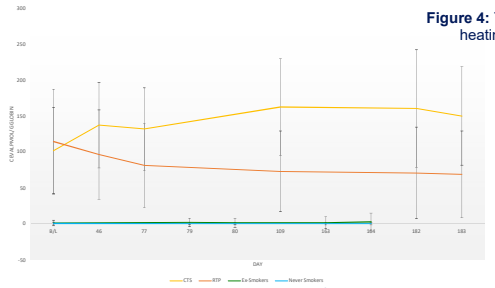

Figure 5: CEVal levels measured by Sheppard et al. [4]

Categorisation of subjects using CEVal levels

Based on data on CEVal levels from a previous study by Sheppard et al.[4] (Figure 5) threshold levels for CEVal were set for the 12-month study to categorise subjects that smoked at around the same level as prior to the study, subjects that either used both glo and continued to smoke (dual use) or subjects in the cessation group that continue to smoke occasionally and finally subjects that were compliant (Table 1).

Table 1: Categorisation of subjects using CEVal levels[5]

- Conservative estimate
- After the study, model will be reviewed with Cessation arm data

Category	Day 90	Day 180	Day 360
Highly Likely Smoking	>164 pmol/g Hb	>112 pmol/g Hb	>78 pmol/g Hb
Potential Dual Use	78 - 164 pmol/g Hb	54 - 112 pmol/g Hb	35 - 78 pmol/g Hb
Potential Solus Use	<78 pmol/g Hb	<54 pmol/g Hb	<35 pmol/g Hb

Results

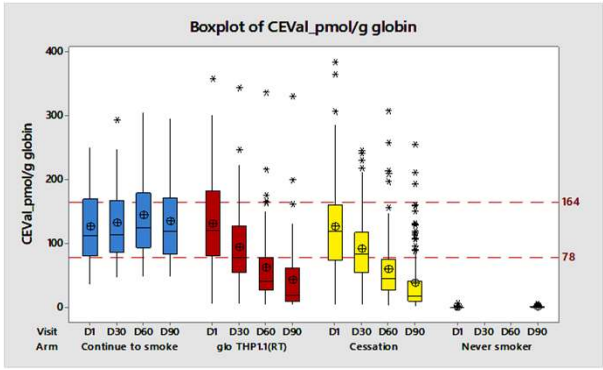

Figure 6: Levels of CEVal for timepoints up to Day 90. Threshold levels as described in Table 1 are also indicated

As shown in Figure 6, on average levels of CEVal clearly are reduced in the glo and smoking cessation groups. Whereas, subjects in the continue to smoke arm show very little change in CEVal levels over 90 days.
In the glo switching arm there were 74 subjects in total, 2 of which were in the non-compliant category and 10 in the dual-use category. This leaves 62 subjects in the compliant category.
For the cessation arm there were a total of 132 subjects with 3 continuing to smoke at similar levels prior to the study and 19 subjects who were smoking occasionally. This leaves a total of 110 subjects in the cessation arm in the compliant category.

Conclusions

This study shows that monitoring CEVal in a switching study, where subjects switch to the glo THP or cease smoking completely, is an effective method for measuring compliance. Further work however, is required to refine the thresholds set for categorising continuing to smoke and dual-product use.

Disclosure
This work was funded in full by British American Tobacco (Investments) Ltd.

References

1. Newland et al. **Internal and Emergency Medicine 2018; 14(6):885-898**
2. Noad et al. **Heart 2016;102:1371–1379.**
3. Harrison et al. **Nutr Metab Cardiovasc Dis 2004; 14:344-350**
4. Sheppard et al **Regulatory Toxicology and Pharmacology 2015; 72:273–291**
5. Camacho et al. **Contemporary Clinical Trials Communications 2020; 17:100535**

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