

## Preliminary Analysis of Blood Nicotine Concentration

### 1.0 Aim

To determine the bioavailability and Cmax of Nicotine from ECOpure preparations using an Intellicig® Nicotine Delivery Device (NDD).

### 2.0 Introduction

ECOpure is a Nicotine containing preparation manufactured in the UK by Intellicig® NDD. ECOpure is manufactured for use in NDDs as a vaporising liquid for direct inhalation into the mouth and lungs. It is available in both 20cc bottles and prepared cartridges. A range of flavours and strengths are also available including a Nicotine free preparation (Zero).

Intellicig® NDD intends to be sold as an NRT in the future and so requires Marketing Authorisation. In order for this to be achieved the product must be made [REDACTED] Final Stability testing must also be carried out on the product to determine the product shelf life although extensive stability testing has already been performed on current preparations.

We propose to do a number of studies, one of which is the study on the current ECOpure preparation to determine whether or not the Nicotine concentration is correct and would be effective as an NRT. For study purposes the Intellicig® will be tested against a tobacco containing cigarette.

Following this study a final preparation of ECOpure will be determined for NRT purposes. Final stability testing can then be carried out, with the ultimate goal [REDACTED]

### 3.0 Sponsor

CN Creative Ltd., Elap House, Fort Street, Accrington, BB5 1QG, UK.

### 4.0 Study Design

A randomised cross-over study to determine Nicotine bioavailability in moderate smokers using an Intellicig® NDD and a tobacco containing cigarette.

On day one of the study Subject Group1 and Subject Group2 will have blood samples collected at time 0 (T=0), immediately prior to smoking a cigarette, to determine blood plasma Nicotine levels prior to smoking. Blood samples will then be taken following the

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smoking of a cigarette at 2 minutes (T=2), 5 minutes (T=5), 7 minutes (T=7), 10 minutes (T=10) and 30 minutes (T=30).

On day two of the study Subject Groups 1 and 2 will have blood samples collected at time 0 (T=0), immediately prior to use of an Intellicig<sup>®</sup> to determine blood plasma Nicotine levels prior to smoking. Blood samples will then be taken following the use of Intellicig<sup>®</sup> at 2 minutes (T=2), 5 minutes (T=5), 7 minutes (T=7), 10 minutes (T=10) and 30 minutes (T=30).



Number of participants: ■

### 5.0 Study Agents

ECOpure Medium Nicotine preparation for use in Intellicig<sup>®</sup> NDD.

Manufacturer: CN Creative Ltd, Elap House, Fort Street, Accrington, BB5 1QG.

Batch Release Site: CN Creative Ltd, UMIC, Biotec Centre, Grafton Street, Manchester, M13 9XX.

### 6.0 Evaluation Criteria

#### 6.1 Safety Criteria

- Participants will be required to fill in a health questionnaire prior to participating in the trial. Participants will be verbally monitored through the duration of the trial for symptoms of Nicotine overdose, primarily headache and nausea.

#### 6.2 Inclusion Criteria

- Informed Consent
- 18 years of age or older
- Current smoker

#### 6.3 Exclusion Criteria

- History of heart disease
- Diabetes mellitus (NIDDM or IDDM)
- Over the age of 65

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- Currently using an NRT product
- Heavy smoker 20+ a day
- General ill health
- Pregnancy

### 6.4 Withdrawal Criteria

- Severe headache
- Nausea
- Other Symptoms of Nicotine overdose
- Light headedness
- Discretion of investigator
- Smoking 12 hours prior testing

### 7.0 Investigators

CN Creative Ltd. will be the investigators for this trial.

### 8.0 Adverse Events

Any adverse events during the study, whether related to the Nicotine preparation or device, will be assessed and recorded by the investigator. Adverse events may be either clinical or laboratory test abnormalities.

Serious adverse events must be reported to CN Creative Ltd. within 24 hours giving as much detail as possible. A complete report must be received within seven days of the adverse events becoming apparent.

Participants may leave the study either at their own wish or at the wish of the investigators. Reasons for participants leaving the trial must be recorded.

### 9.0 Necessary Approvals



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### 10.0 Study Monitoring

All data remains the property of CN Creative Ltd. No publication in part or whole is permitted to be made without prior written consent from CN Creative Ltd.

### 11.0 Laboratory Analysis

Blood Samples will be drawn by Dr. [REDACTED]

[REDACTED] Laboratories will carry out blood sample analysis.  
 Laboratories, [REDACTED]

### 12.0 Results

Results from Blood Plasma Nicotine concentration show an average Cmax for the Intellicig® NDD to be [REDACTED] ng/mL. Cmax for 0.5mg cigarette were observed to be at [REDACTED] ng/mL. Cmax was reached at similar times for both the cigarette and Intellicig® NDD with the average time taken to reach Cmax at 7minutes.

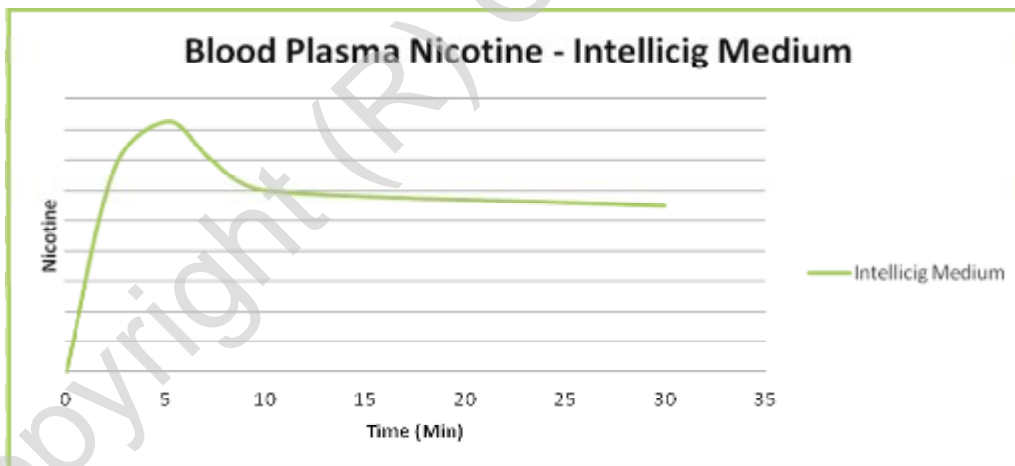


Figure 1 – Rate of absorption of Nicotine from Intellicig in venous blood

From Figure 1 above it is evident that there is a steep initial rate of absorption between 2 and 5 minutes with the gradient of the line equating to [REDACTED]. The sharp rise in Nicotine concentration observed is understood to be responsible for alleviating Nicotine withdrawal symptoms and satisfying the craving at the nicotine receptor level. It is this sharp rise in Nicotine level that is absent from many NRT's currently available and it is precisely this which is thought to alleviate Nicotine withdrawal cravings.

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The rate of absorption when the same group smoked a cigarette containing 0.5mg of Nicotine was seen to share similar kinetics to that of the Intellicig® NDD

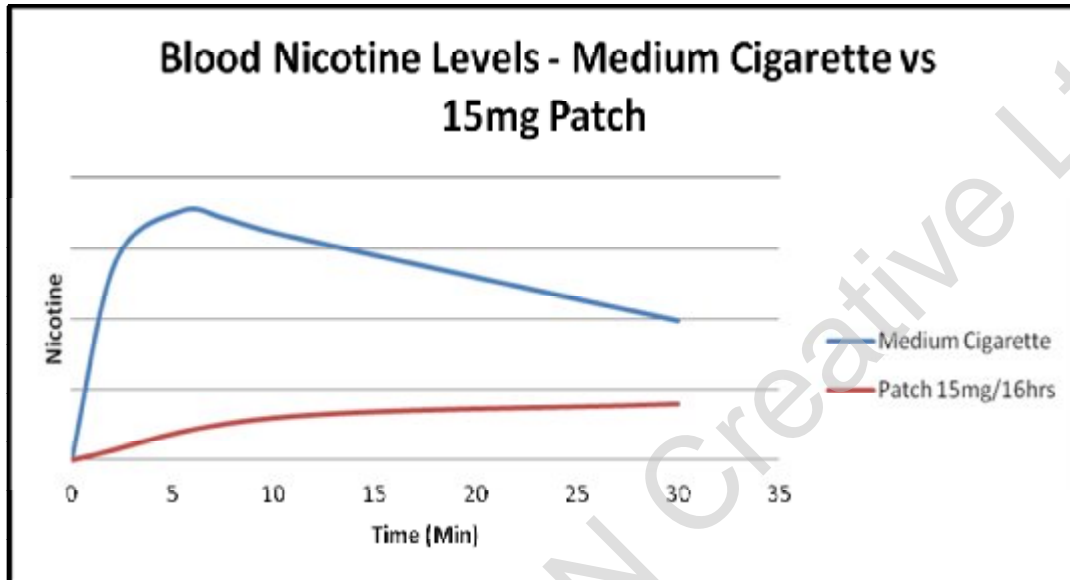


Figure 2 - Comparison of rate of absorbance of Medium Cigarette and 15mg Patch

From Figure 2 it can be observed that Nicotine absorption from cigarettes occurs at a with a Cmax at 5.4 minutes (compared to a Cmax at 5.1 minutes for the Intellicig® NDD) A comparison may also be made from published data on a Nicotine containing patch (15mg) designed to deliver Nicotine over 16hours. Analysis of the rate of absorption of the patch shows a slow rate of absorbance with a Cmax at approximately 5 hours (not shown in graph above).

	Cigarette 0.5mg	Intellicig® NDD	NiQuitin™ Lozenge 4mg*	Nicorette® Gum 4mg*
Time of Cmax [units: (hours)] Median (Full Range)	0.13 (0.083 to 0.16)	0.1 (0.08 to 0.12)	0.75 (0.17 to 2.02)	0.50 (0.33 to 1.00)

Table 1 – Comparison of Cmax of Cigarette, Intellicig®Med NDD, NiQuitin™ Lozenge and Nicorette® Gum 4mg

\*Information derived from published data.

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### 13.0 Conclusion

From the above results it is possible to conclude that the Intellicig<sup>®</sup> NDD delivers a dose of Nicotine to the body which has a distinct C<sub>max</sub>. It is this peak in Nicotine concentration in the blood which is thought to be responsible for alleviating Nicotine cravings. Nicotine concentration must reach a threshold in the brain before receptor activation of the Dopamine reward system may occur and alleviate the symptoms associated with Nicotine withdrawal.

Comparison of the C<sub>max</sub> of Intellicig<sup>®</sup> NDD and a 0.5mg Cigarette show similarities in time with only a 12 second time difference in time taken to reach C<sub>max</sub>. Comparison of these results with published data on Marketed NRT products suggests the Intellicig<sup>®</sup> NDD can deliver Nicotine at a much quicker rate than that of currently marketed NRT products.

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