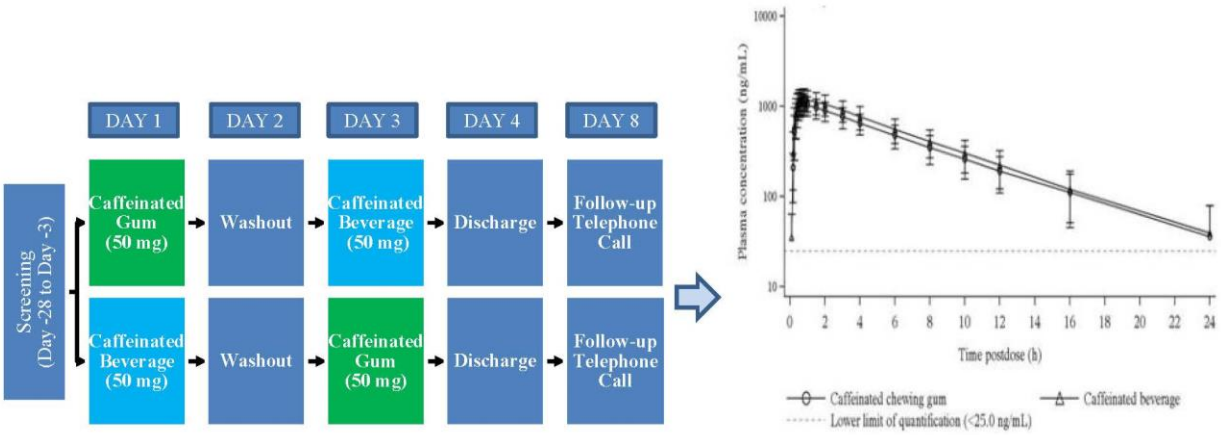
**Title**: A Randomized, 2-Way Crossover Study to Evaluate the Pharmacokinetics of Caffeine Delivered via Caffeinated Chewing Gum versus a Marketed Caffeinated Beverage in Healthy Adult Volunteers*




**Endpoint: Pharmacokinetic profiles of caffeine administered by the caffeinated gum and beverage were similar**

* This study has been submitted to a peer-reviewed journal, with online publication anticipated this fall.

**Background**: Caffeine is the most commonly consumed stimulant in the world (**1, 2**) and is often the chosen means to maintain alertness and counteract the effects of sleep deprivation and fatigue. The impact on consumer health has been extensively studied (**2**).

The vast majority of studies investigating the safety of caffeine were conducted following exposure to known doses of caffeine administered as food, beverages, or oral medications for which the kinetics of intestinal absorption are well characterized. Recently, new formulations for delivery of caffeine have been developed, including caffeine-containing chewing gum (**3,4**). However, because administration of caffeine via gum entails the absorption of caffeine through the mucosal membranes of the mouth, the pharmacokinetics (PK) of which is less well characterized than that of intestinal absorption.

This study sought to compare the PK of caffeine administered as a chewing gum pellet containing approximately 50 mg caffeine with that following consumption of a marketed caffeinated beverage (instant coffee) at approximately the same strength per serving.

**Methods**: This was a controlled open-label, randomized, two-period crossover study. The study was conducted at Covance Clinical Research Unit, Inc. in accordance with Good Clinical Practices. A total of 16 healthy male or female adults were enrolled in the study. Caffeinated chewing gum and a serving of instant coffee, each containing approximately 50 mg caffeine were administered with blood samples collected prior to and up to 24 hours after administration start. Plasma caffeine levels were analyzed using validated LC MS/MS methodology.

Non-compartmental and compartmental modeling was used to determine caffeine PK parameters following the administration of each product (**5**). The maximum observed concentration ($C_{max}$) and the time to reach $C_{max}$ ($t_{max}$) were obtained from the concentration-time profile. The area under the concentration-time curve (AUC) from Hour 0 to the time of the last measurable concentration ($AUC_{0-t}$), AUC extrapolated to infinity ($AUC_{0-\infty}$) and absorption rate constant ($k_a$) were determined. Dose-normalized (DN) values for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ were calculated by dividing the calculated PK parameters by the actual received dose (mg).

**Results and Discussion.** There were no statistical differences between the two caffeine products in $t_{max}$ ($P = 0.3308$) and $k_a$ ($P = 0.3894$). Although formulated at approximately 50 mg caffeine each, mean dose released from chewing gum was approximately 18% less than beverage. In order to account for the differences in actual dose administered between the two caffeine products, the PK parameters were dose-normalized to allow statistical comparison and determine relative bioavailability. While there were differences in exposure (DN $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$), the differences were not significantly different between the delivery methods and the 90% CIs for the ratios of AUC and $C_{max}$ fell within the recommended range for product bioequivalence suggested by the FDA of 80% to 125% (**6**) (**Table**). No product-related adverse events (AEs) were reported following caffeine administration by either gum or beverage.

The results indicate that there is no marked difference in the PK profile of caffeine delivered by the two products. These findings are in part supported by those previously reported by (**3**) who found that at doses of 50 to 200 mg, caffeine administered by chewing gum gave a comparable exposure to that delivered by capsule. The PK profiles of caffeine administered by the chewing gum and beverage were similar, suggesting that the body of scientific literature on caffeine, which is mostly based on data from caffeinated beverages, can be leveraged to support the safety of caffeine delivered via chewing gum. Furthermore, current maximum safe dose advice for caffeine issued by health regulatory authorities should be applicable whether the dose is administered via chewing gum or by oral administration of caffeinated food or beverages.

**Conclusions**: The PK profiles of caffeine administered by the chewing gum and beverage were similar. Existing scientific literature on caffeine, based mostly on data from caffeinated beverages, can be leveraged to support the safety of caffeine delivered via chewing gum and current maximum safe caffeine dose advice should be applicable irrespective of delivery method.

## References


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**Table.** Summary of the Pharmacokinetic Parameters for Caffeine

| Parameter (Unit) | Treatment | N | Geometric least squares means | Ratio of geometric least squares means (Test:Reference) | 90% CI for the ratio (Test:Reference) Lower | Upper | P-value |
|---|---|---|---|---|---|---|---|
| DN $AUC_{0-t}$ (h*ng/mL/mg) | Caffeinated chewing gum[Test] | 15 | 172 | | | | |
| | Caffeinated beverage[Reference] | 16 | 160 | 1.07 | 1.04 | 1.11 | |
| DN $AUC_{0-\infty}$ (h*ng/mL/mg) | Caffeinated chewing gum[Test] | 15 | 183 | | | | |
| | Caffeinated beverage[Reference] | 16 | 168 | 1.09 | 1.05 | 1.13 | |
| DN $C_{max}$ (ng/mL/mg) | Caffeinated chewing gum[Test] | 15 | 28.7 | | | | |
| | Caffeinated beverage[Reference] | 16 | 25.7 | 1.12 | 1.04 | 1.20 | |
| $t_{max}$ (h) | Caffeinated chewing gum[Test] | 15 | 0.67 | | | | |
| | Caffeinated beverage[Reference] | 15 | 0.58 | -0.08 | -0.17 | 0.08 | 0.3308 |
| $k_a$ (1/h) | Caffeinated chewing gum[Test] | 15 | 2.36 | | | | |
| | Caffeinated beverage[Reference] | 15 | 2.60 | 0.33 | -0.36 | 1.15 | 0.3894 |

Abbreviations: CI = confidence interval; DN $AUC_{0-t}$ = dose-normalized area under the concentration-time curve (AUC) from Hour 0 to the last measureable concentration; DN $AUC_{0-\infty}$ = dose-normalized AUC extrapolated to infinity; DN $C_{max}$ = dose-normalized maximum observed concentration; $k_a$ = absorption rate constant; N = number of subjects; $t_{max}$ = time of the maximum observed concentration.

Notes: One subject was excluded from chewing gum treatment since the quantifiable pre-dose value was >5% of $C_{max}$ value. Only paired data was presented and statistically analyzed for $t_{max}$ and $k_a$. Least square means and 90% confidence interval are based on a linear mixed effects model with treatment as a fixed effect and subject as a random effect. The ratio and corresponding confidence limits are back-transformed from the original difference and confidence