The purpose of our study was to evaluate the effect of transient heat exposure on \textit{in vitro} permeation of lidocaine in excised human skin and \textit{in vivo} bioavailability in healthy human volunteers under harmonized study conditions. A central consideration in the study design was to evaluate the influence of exposure to elevated heat early in the wear duration before steady-state is achieved compared with exposure to elevated heat later in the wear duration after steady-state has been achieved.

An open-label, six-way crossover pharmacokinetic study was conducted on healthy human subjects. Skin temperature of 42 ± 2°C was achieved by application of a heating pad over the patches. Early heat was applied for 90 mins, 4 hours post-patch application and late heat was applied for 90 mins, 8.5 hours after application. Pharmacokinetic profile in the absence of heat application was obtained. Similar study design was used for \textit{in vitro} permeation tests (IVPT) performed using \textit{ex vivo} human skin to investigate dermal absorption from two patches. A circulating water bath was used to mimic heat exposure.

A 2.0 – 4.5 fold and a 1.8 – 4.3 fold enhancement in \(J_{\text{max}}\) was observed with early and late heat application. A 5.0 – 6.2 fold and a 2.3 – 2.5 fold enhancement in \(C_{\text{max}}\) was observed with early and late heat application respectively. The observed \textit{in vivo} concentrations were de-convoluted to obtain the fraction of drug absorbed. The correlation between fraction absorbed \textit{in vivo} and fraction permeated \textit{in vitro} for the baseline study arm was described by a polynomial equation. Heat factor was incorporated into the equation to predict the heat-induced enhancement in lidocaine bioavailability.

IVPT studies performed under the same conditions as those of interest \textit{in vivo} may have the potential to correlate with and be predictive of \textit{in vivo} results, and may have the utility to evaluate heat effects \textit{in vitro}. 