In Vivo Pharmacokinetic Evaluation of a Sublingual Semaglutide Compounded Formulation (SubMagna™ SL HMW): Pilot Study in an Animal Model

SUMMARY: A compounded formulation of sublingual semaglutide in PCCA SubMagna SL HMW was prepared for *in vivo* pharmacokinetics evaluation. In this pilot study, it was observed that semaglutide is detected in the blood plasma as soon as 5 minutes after sublingual administration. There were no adverse effects observed.

Introduction:

Semaglutide delivered sublingually is a potential alternative route of administration that overcomes the extremely low absorption of the oral tablets and the inconvenience of the injectable medications. A compounded formulation of sublingual semaglutide in PCCA SubMagna SL HMW was prepared for *in vivo* pharmacokinetics evaluation. The purpose of this study was not to determine the appropriate sublingual dose of semaglutide but, instead, to evaluate the ability of the proprietary base to deliver the peptide into the blood system by means of a sublingual dosage form.

Methodology:

The *in vivo* evaluation test was conducted by GemPharmatech Co., Ltd following ethics approval: animal protocol CDAP20240621-1#; project number PO-GJC0520240500076-01. The test product semaglutide (Rybelsus®) $6x10^6$ ng/mL compounded formulation (SubMagna SL HMW) was provided by PCCA. SD (Sprague–Dawley) rats (5-8 weeks, male) (n=3) were divided in two groups according to body weight: G1 (control group, n=1, SubMagna SL HMW only) and G2 (test group, n=2, sublingual semaglutide compounded formulation). Following 12 hr of fasting and 1.5 hr of deprivation of water, the rats were administered 1 mg/kg of SubMagna SL HMW (G1) or the sublingual semaglutide compounded formulation (G2) (day 0). All rats were fasted for 4 hr and deprived of water for 2 hr after administration. Blood collection by jugular vein catheter occurred at the following time-points: 0 min (pre-dosing), 5 min, 15 min, 30 min, 1 hr, 1.5 hr, 2 hr, 4 hr, 8 hr, 24 hr (day 1), and 48 hr (day 2), as shown in Figure 1. The plasma samples were analyzed for LC-MS/MS detection of semaglutide. All rats were observed for signs of adverse effects after administration. The observations included general activity, fur, head, feces, body weight and body temperature. The rat in G1 was monitored for 7 days.

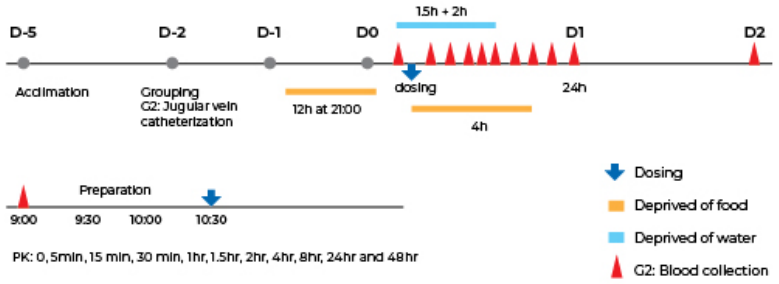

Figure 1. Study timeline and description for the *in vivo* pharmacokinetics evaluation of a sublingual semaglutide compounded formulation.

Results and Discussion:

Semaglutide was detected in the blood plasma of the rats in the test group (G2) as soon as 5 minutes after sublingual administration. As shown in Figure 2, the highest levels of semaglutide were registered at 1 hr post-administration (8.8 ng/mL). The calculated half-life from the two rats was 6.3 hr, which is similar to the reported half-life in a published study using these animals. All rats increased in weight throughout the study according to the expected growth curve of the SD strain. This is an important parameter that indicates a good health profile in both groups. All rats completed the study and there were no adverse effects observed. This *in vivo* pharmacokinetics evaluation of a sublingual semaglutide compounded formulation, although preliminary, shows clear evidence to support that semaglutide is effectively absorbed sublingually. This is a pilot study due to the limited number of rats tested. As such, statistical analysis was not performed, and further studies are needed for a quantitative evaluation. A full-scale single-dose pharmacokinetics study in rats is currently ongoing and the results will be available soon.