A Single-Dose Pharmacokinetic Study of Sublingually Delivered Semaglutide in SubMagna® in Rats

SUMMARY: The previous pilot pharmacokinetic study has demonstrated the absorption of semaglutide via sublingual route using SubMagna. The objective of this study is to compare the pharmacokinetic profile of sublingually delivered semaglutide in SubMagna with that of oral and injectable products. Results showed that semaglutide in SubMagna resulted in less variability in plasma concentrations and improved bioavailability compared to oral commercial tablet.

Introduction:

SubMagna® SL HMW was designed to efficiently deliver a wide range of drugs with varying molecular weights — including high molecular weight (HMW) substances. SubMagna was initially developed as an alternative dosing form for commercially available semaglutide in nonsterile compounded preparations. This proof-of-concept study aims to demonstrate the sublingual absorption of semaglutide from SubMagna and to compare its pharmacokinetic profile with that of commercially available oral and injectable products.

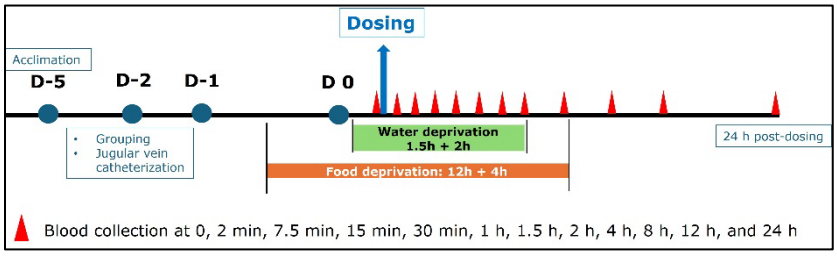

Figure 1. *Summary of the study timeline.*

Methodology:

The animal study was conducted by GemPharmatech Co., Ltd following ethics approval: animal protocol CDAP20240621-1#; project number PO-GJC0520240500076-02. The test product semaglutide (API from commercial Rybelsus® tablets) $6x10^6$ ng/mL compounded formulation (SubMagna SL HMW) was provided by PCCA. Sprague–Dawley rats (5-8 weeks old, male) (n=24) were randomly assigned to treatment groups as shown in Table 1. The dosing and sampling schedule is present in Figure 1. All rats were fasted 12 hours prior to dosing and for 4 hours post-dosing. Water deprivation started 1.5 hours before dosing and resumed 2 hours afterward. The plasma samples were analyzed for semaglutide using LC-MS/MS.

Treatment	Dose	Route	Frequency	Number of Rats
Commercial (Semaglutide injection)	0.01 mg/kg	Subcutaneous	Single dose	6
Semaglutide in SubMagna	1 mg/kg	Sublingual	Single dose	6
Commercial (Semaglutide tablets)	1 mg/kg	Oral	Single dose	6
Commercial (Semaglutide tablets)	20mg/kg	Oral	Single dose	6

Table 1. *Summary of the treatment groups.*

Results:

Semaglutide was detected in all rats as early as 2 minutes post-dosing. The variability in plasma concentrations among individual rats and pharmacokinetic parameters was analyzed.

Variability

Consistent with findings in humans, oral semaglutide produces large variability in plasma concentrations of semaglutide in rats. In contrast, sublingual dosing results in smaller variability as shown in Figure 2, with the smallest variability observed following subcutaneous injection.

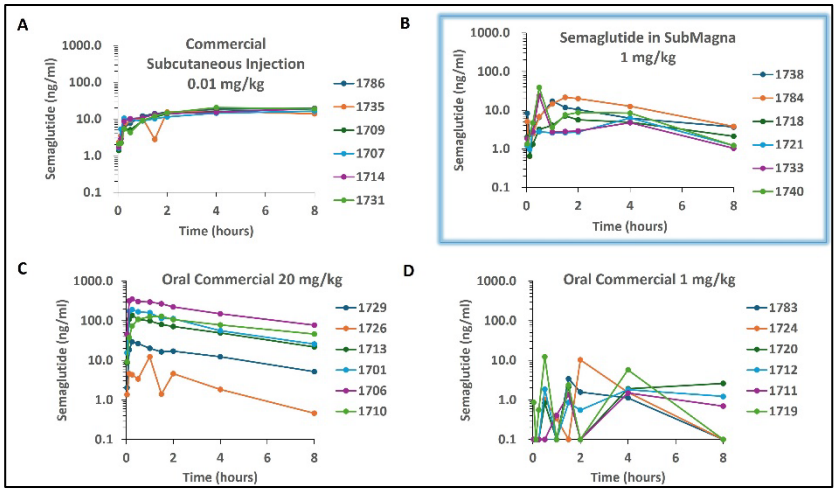

Figure 2. *Plasma concentrations of semaglutide in different treatment groups. Each line represents data from an individual rat, labeled with its ID.*

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Absorption / AUC

When comparing the area under the plasma concentration-time curve (AUC) over 24 hours, as shown in Figure 3, the sublingual group exhibited a significantly higher AUC than the oral tablet 1 mg/kg group. The AUC in oral tablet 20 mg/kg group was not shown in the bar graph due to considerable variability ranging from 29.34 ng*h/ml to 2077.24 ng*h/ml.

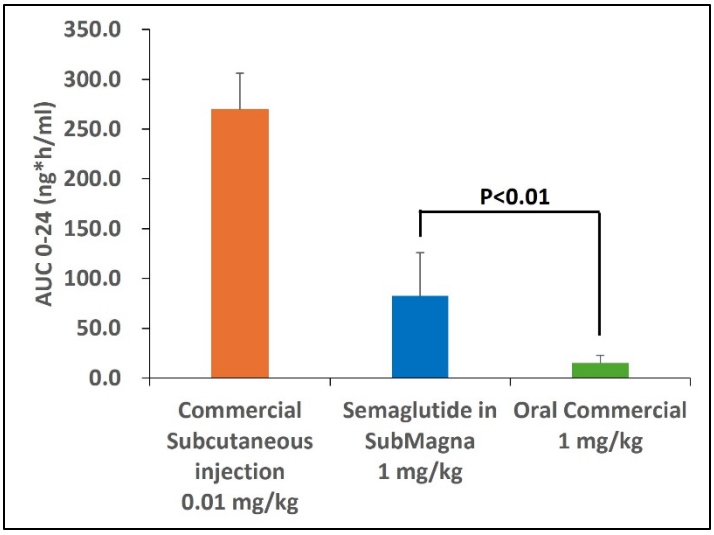

Figure 3. *AUC of semaglutide in different treatment groups.*

C_{max} & T_{max}

Semaglutide in SubMagna demonstrates a similar absorption profile compared to the oral group, both reaching C_{max} as early as 30 minutes post-dosing as shown in Figure 4 (right panel). This is distinct from the subcutaneous route, which reaches a prolonged peak at 8 hours (Figure 4**,** left panel).

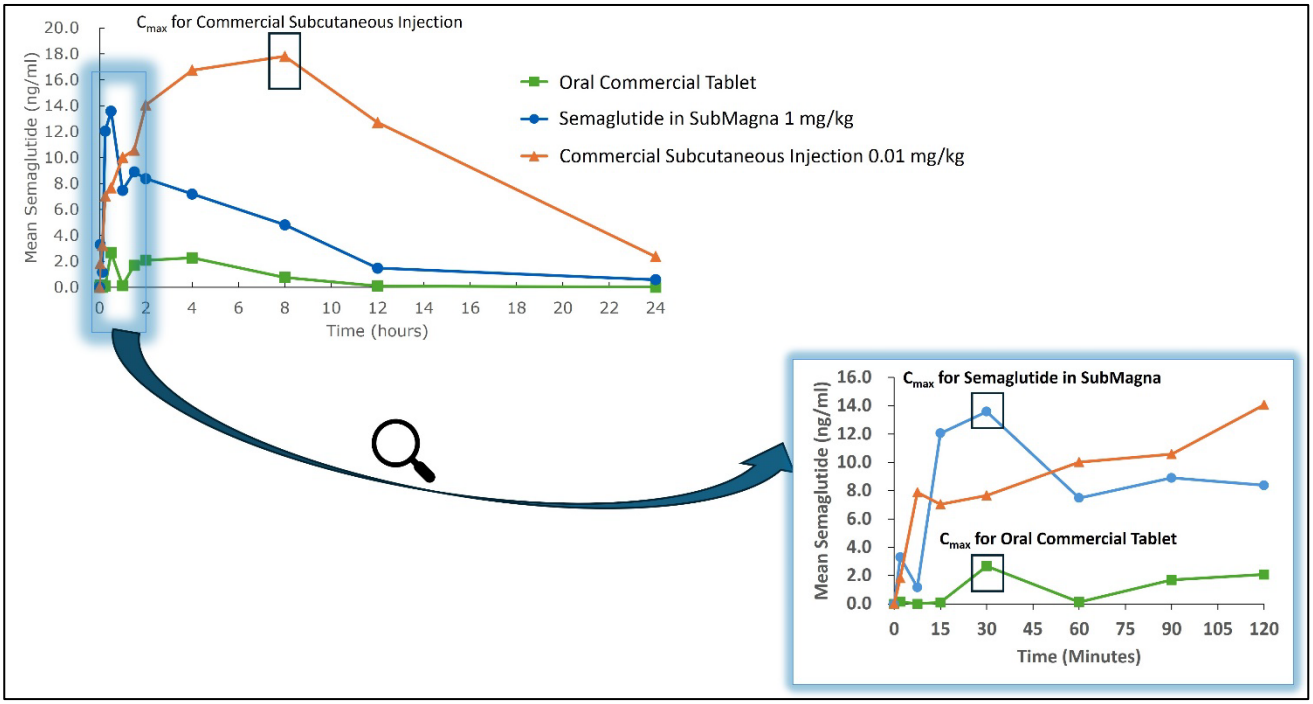

Figure 4. *Mean plasma concentration-time profile of semaglutide in different treatment groups. C_{max} of injection group was labeled in the left panel. C_{max} of sublingual and oral groups were labeled in a zoomed-in view of the first 120 minutes post-dosing (right panel).*

Relative Bioavailability

Relative bioavailability was calculated based on the absorption of semaglutide in different dosage forms versus semaglutide in commercial injection using the data in Table 2. Sublingual administration shows significantly higher bioavailability compared to both oral groups. There is no significant difference in bioavailability between the oral 1 mg/kg and 20 mg/kg groups.

Drug	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (Range) (ng/mL)	AUC_{0-24} (Range) (ng*h/mL)	$t_{1/2}$ (h)	Relative Bioavailability (F) (%)
Commercial Injection	Subcutaneous	0.01	8	17.8 (16.3-20.3)	269.85 (211.97-302.77)	5.27	100
Commercial Tablet	Oral	20	0.25	131.3 (12.3-352.0)	798.02 (29.34-2077.24)	5.82	0.163
	Oral	1	0.5	2.7 (1.5-12.3)	15.08 (7.05-27.58)	5.22	0.061
Semaglutide	**Sublingual in SubMagna**	**1**	**0.5**	**13.6 (6.3-38.5)**	**82.53 (43.02-138.93)**	**5.88**	**0.336**

Table 2. *Summary of pharmacokinetic parameters and calculated relative bioavailability of semaglutide in different treatment*

Conclusion:

This single-dose pharmacokinetic study further validated SubMagna's ability to deliver semaglutide sublingually. Sublingual delivery by SubMagna demonstrated less variability in plasma concentrations and absorption compared to the oral commercial tablet. The findings suggested improved bioavailability for semaglutide in SubMagna versus the oral commercial tablet. The C_{max} /T_{max} profiles for sublingual and oral administration are similar, indicating that the dosing frequency for sublingual should be similar to that of oral dosing.

This proof-of-concept study is not intended to provide guidance on the sublingual dosing of semaglutide in SubMagna in humans, or dosing conversion from oral or injectable forms to sublingual administration. Further pharmacokinetic studies in humans, along with dose-finding studies, are necessary to determine the equivalent sublingual dose in humans