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

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

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.

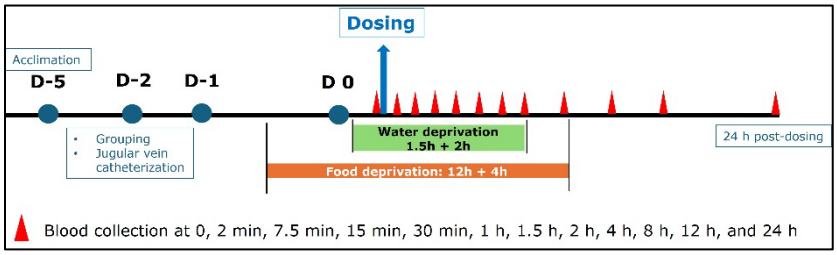

Figure 1. *Summary of the study timeline.*

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 (Rybelsus®) 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
Ozempic® (Semaglutide injection)	0.01 mg/kg	Subcutaneous	Single dose	6
Rybelsus® in SubMagna	1 mg/kg	Sublingual	Single dose	6
Rybelsus® (Semaglutide tablets)	1 mg/kg	Oral	Single dose	6
Rybelsus® (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 were analyzed.

Variability

Consistent with findings in human, oral Rybelsus® 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.

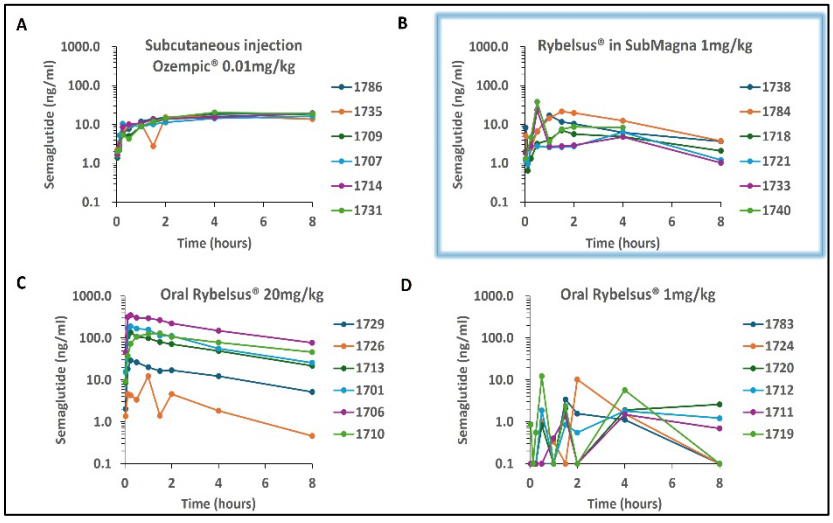

Figure 2. *Plasma concentrations of semaglutide in different treatment groups. Each line represents data from an individual rat, labeled with its ID.*

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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 Rybelsus® 1 mg/kg group, while considerable variability was observed in oral Rybelsus® 20 mg/kg group.

C_{max} & T_{max}

Rybelsus® 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).

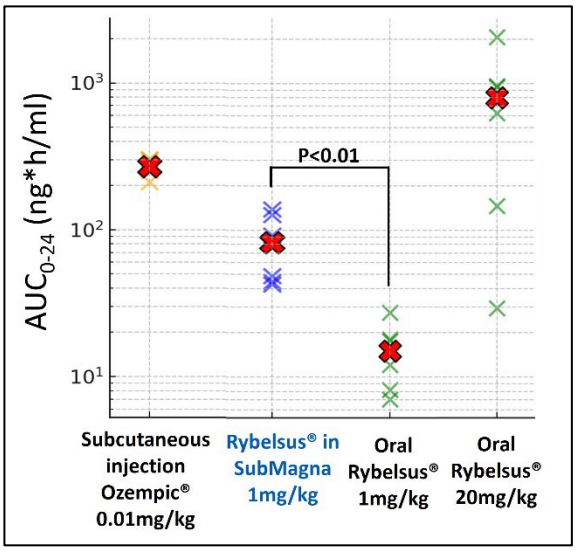

Figure 3. *AUC of semaglutide in different treatment groups. Each "X" symbol represents the AUC value for an individual rat, with red "X" symbols indicating the mean values.*

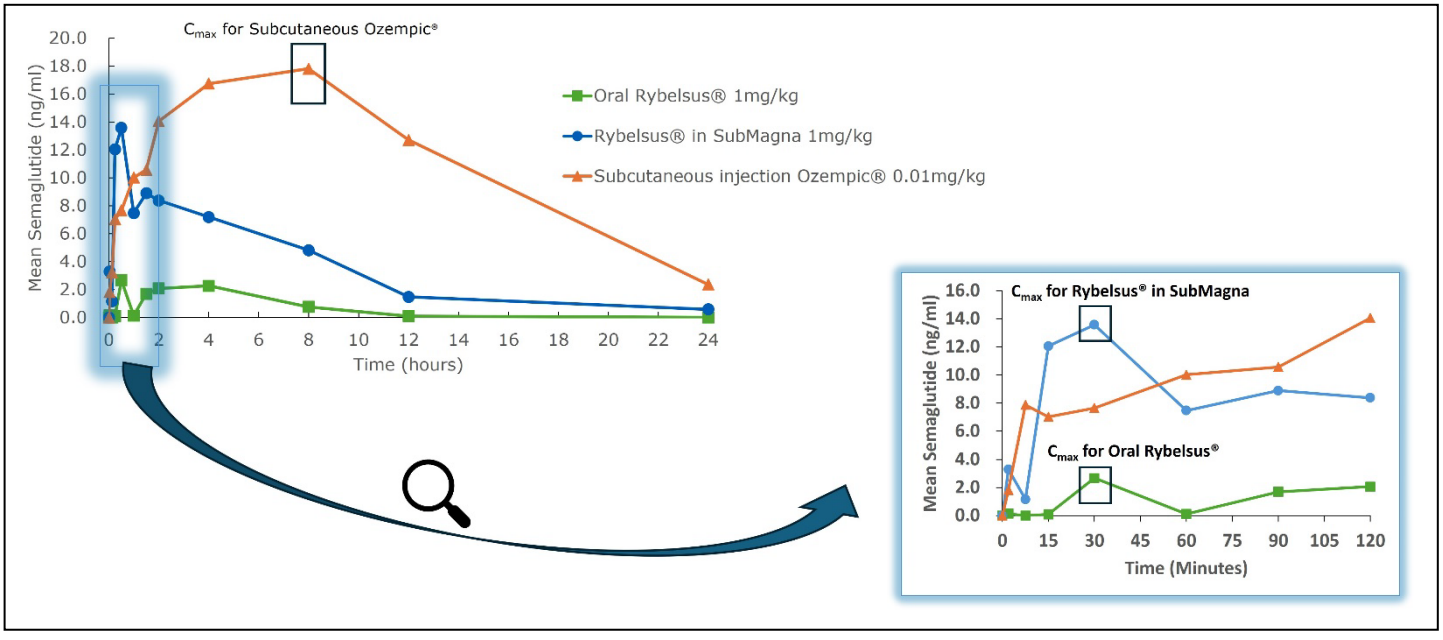

Figure 4. *Mean plasma concentration-time profile of semaglutide in different treatment groups. C_{max} of injection group was labeled in the left panel. C_{max} of sublingual and oral groups were labeled in a zoomed-in view of the first 120 minutes post-dosing (right panel).*

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Relative Bioavailability

Relative bioavailability was calculated based on the absorption of oral Rybelsus® versus Rybelsus® in SubMagna using the data in Table 2. Sublingual administration shows significantly higher bioavailability compared to both oral groups, as shown in Figure 5. There is no significant difference in bioavailability between the oral 1 mg/kg and 20 mg/kg groups.

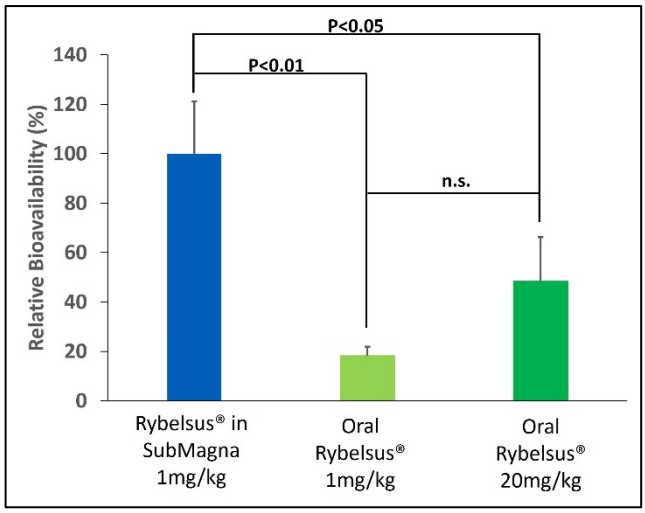

Figure 5. *Relative bioavailability of semaglutide in different treatment groups. Error bars represent the standard error of the mean.*

Drug	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	$t_{1/2}$ (h)
Ozempic®	Subcutaneous	0.01	8	17.8 (16.3-20.3)	269.85 (211.97-302.77)	5.27
Rybelsus®	Oral	20	0.25	131.3 (12.3-352.0)	798.02 (29.34-2077.24)	5.82
	Oral	1	0.5	2.7 (1.5-12.3)	15.08 (7.05-27.58)	5.22
	Sublingual in SubMagna	**1**	**0.5**	**13.6 (6.3-38.5)**	**82.53 (43.02-138.93)**	**5.88**

Table 2. *Summary of pharmacokinetic parameters of semaglutide in different treatment groups.*

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 oral Rybelsus®. The findings suggested improved bioavailability for Rybelsus® in SubMagna versus oral Rybelsus®. 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 Rybelsus® in SubMagna™ in human, 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 human.