iX Biopharma SL Semaglutide (iXB 401)	Technical Report

A Single-Dose Pharmacokinetic Study of a Novel Sublingual Semaglutide Wafer in Rats

SUMMARY: The objective of this study was to compare the pharmacokinetic profile of iXB 401, a sublingually administered semaglutide wafer with that of the orally administered semaglutide tablet, Rybelsus®.
This pharmacokinetic study demonstrated ~20 times greater bioavailability and less variability from the sublingual absorption of semaglutide with iXB 401 compared to the oral absorption of semaglutide with Rybelsus®.

iXB 401

iXB 401 is a novel, sublingual semaglutide wafer which utilizes iX Biopharma's patented sublingual drug delivery technology. The wafer matrix incorporates a proprietary formulation of permeation enhancers and mucoadhesive components designed to enhance sublingual absorption and systemic bioavailability.

Methodology

The animal study was conducted by Eurofins Advinus Biopharma Services, a test facility registered by the Committee for the Control and Supervision of Experiments on Animals (CCSEA), in accordance with the protocol approved by institutional Animal Ethics Committee (IAEC).

Sprague–Dawley rats (7-10 weeks old, weighing 300-350g) were randomly assigned to either iXB 401 sublingual wafer, 10mg/kg (n=6) or oral Rybelsus® tablet, 10mg/kg (n=6) in 1:1 ratio. Animals were anesthetized during sublingual administration to ensure the wafer remained in situ. Venous blood sampling was obtained over an 8-hour period. The dosing and sampling schedule is shown in Figure 1. All rats were fasted overnight prior to dosing. The plasma samples were analyzed for semaglutide using LC-MS/MS.

Results

Plasma semaglutide concentrations reached therapeutic levels as early as 5 minutes post administration (mean: 167ng/mL) with iXB 401 and remained at therapeutic levels throughout the 8-hour pharmacokinetic sampling period.

iXB 401 produced less variability in plasma concentrations of semaglutide in rats (mean CV, 87%) compared to oral Rybelsus® tablets (mean CV, 141%). See Figure 2.

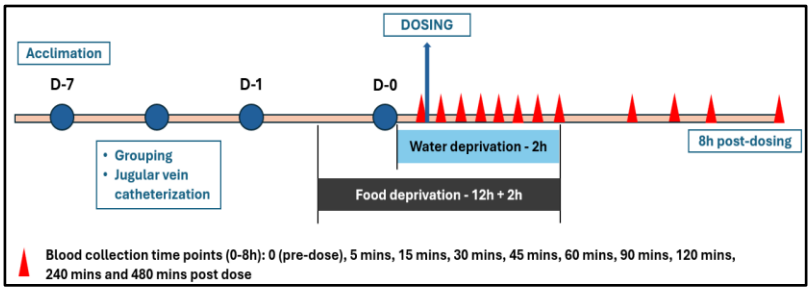

Figure 1. *Summary of the study timeline*

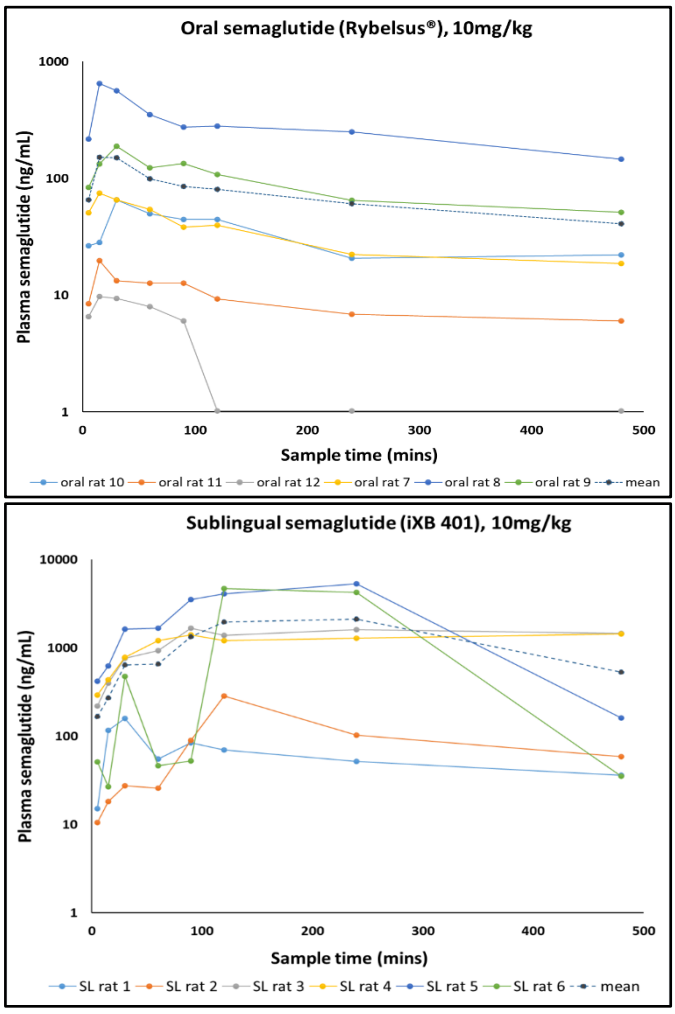

Figure 2. *Plasma concentrations of semaglutide in different treatment groups. Each line represents data from an individual rat.*

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Absorption / AUC

When comparing the area under the plasma concentration-time curve (AUC) over 8 hours, as shown in Figure 3, the iXB 401 group exhibited a significantly higher AUC than the oral Rybelsus® group. Sublingual semaglutide $AUC_{0\text{-}8h}$ was 11,000 ng*h/mL compared to 553 ng*h/mL with oral Rybelsus® tablet (p value < 0.005).

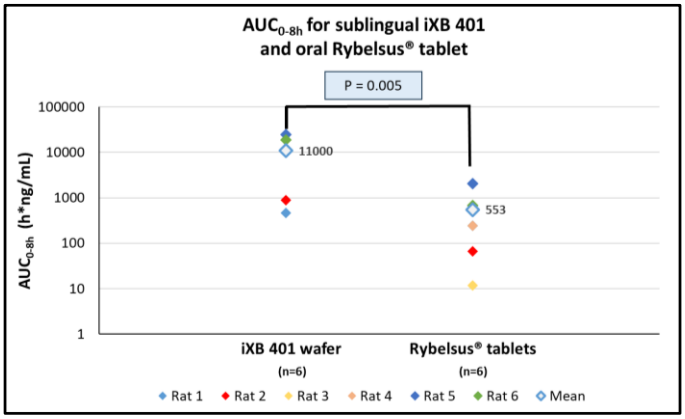

Figure 3. *AUC of semaglutide in different treatment groups. Each dot symbol represents the AUC value for an individual rat, indicating the mean AUC values for each group.*

C_{max} & T_{max}

Rybelsus® tablet demonstrates a similar absorption profile compared to the sublingual wafer group, both reaching Cmax as early as 20-30 minutes post-dosing as shown in Figure 4 (right panel). However, the sublingual group also had a second peak at 240 mins, most likely due to delayed absorption of semaglutide via lymphatic system.

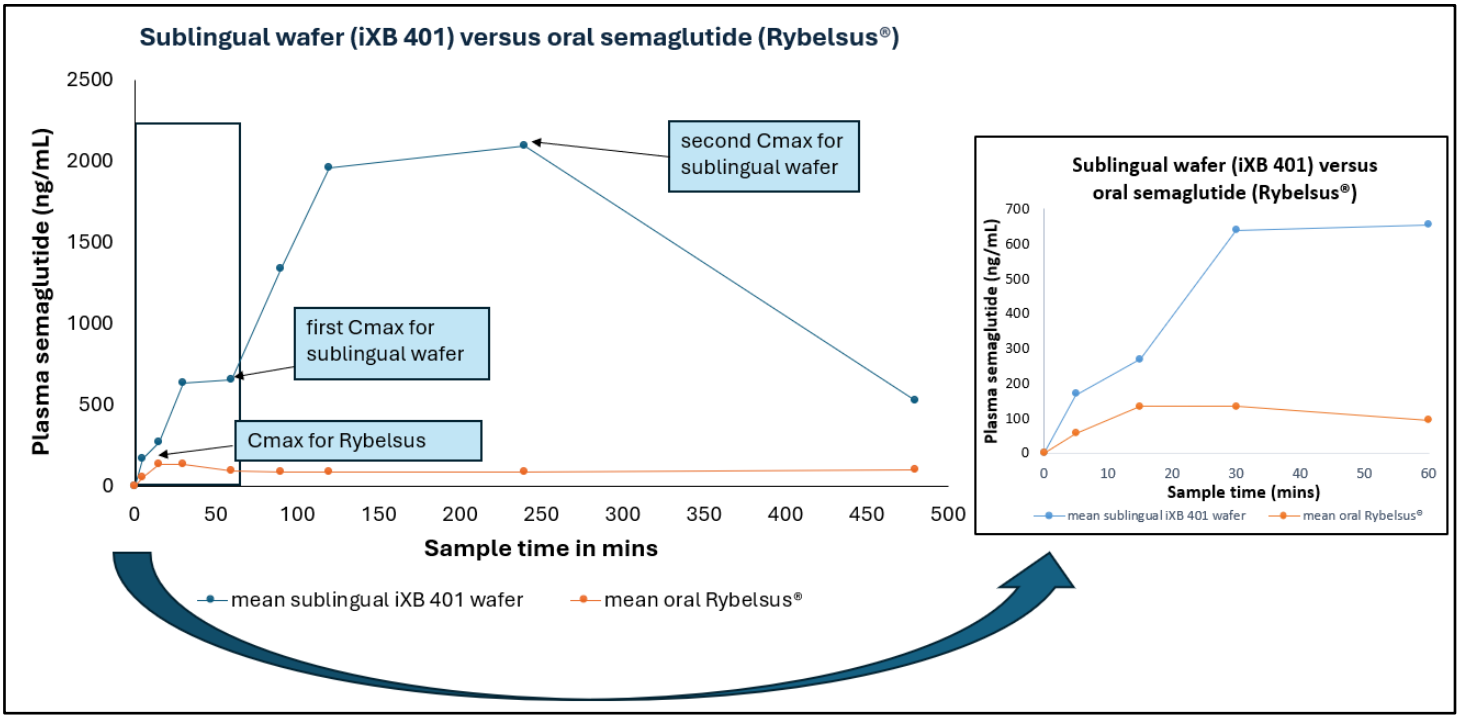

Figure 4. *Mean plasma concentration-time profile of semaglutide in different treatment groups. Cmax of sublingual iXB 401 and oral Rybelsus® groups were labeled in a zoomed-in view of the first 60 minutes post-dosing (right panel). Notice the two peaks (Cmax) for sublingual semaglutide at Tmax 30mins and 240mins*

Relative Bioavailability

Relative bioavailability was calculated based on the absorption of sublingual iXB 401 wafer versus oral Rybelsus® tablets using the data shown in Table 1.

iXB 401 achieved significantly higher bioavailability (~20 times greater) compared to oral Rybelsus®

Drug	Route	Dose (mg/Kg)	T_{max} (mins)	C_{max} (ng/mL)	AUC_{0-8} (ng*h/mL)	Relative Bioavailability
Rybelsus®	Oral	10	20	168	553	100%
iXB 401	**Sublingual**	**10**	**30 (1st), 240 (2nd)**	**2,250**	**11,000**	**1989%**

Table 1. *Summary of pharmacokinetic parameters of semaglutide for iXB 401 and oral Rybelsus®.*

Conclusion

This single-dose pharmacokinetic study demonstrated that iXB 401 sublingual wafers effectively delivered semaglutide systemically in Sprague-Dawley rats. The findings showed an improved relative bioavailability for sublingual semaglutide versus oral semaglutide tablet by ~20 times. Sublingual delivery resulted in less variability in plasma concentrations and absorption compared to oral Rybelsus®. These data are most encouraging for the further development of iXB 401 and suggest potential for use of a lower dose of semaglutide in this novel, non-invasive and convenient dosage form.