BioLingus' Sublingual Technology Use Case

In the 1990s, Thomas Ko developed Immulin in Australia. Manufactured in New Zealand, Immulin is a sublingual type I interferon therapy to treat chronic viral hepatitis, which was sold in China and Kenya.

Subsequently, the technology used to deliver type I interferon sublingually has been taken in pre-clinical animal models in cancer treatment.

Taken together, this provides proof-of-concept that BioLingus' sublingual delivery technology can effectively deliver a protein like interferon to produce systemic effects.

cells

Cells **2021**, *10*, 845

Article

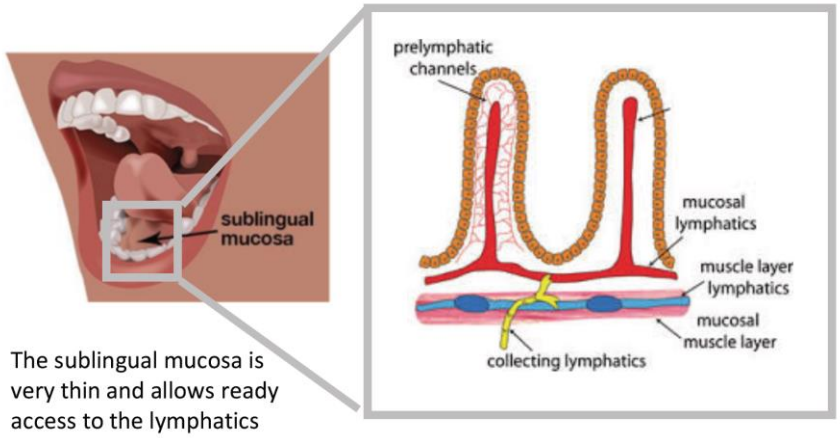
Anticancer Effects of Sublingual Type I IFN in Combination with Chemotherapy in Implantable and Spontaneous Tumor Models

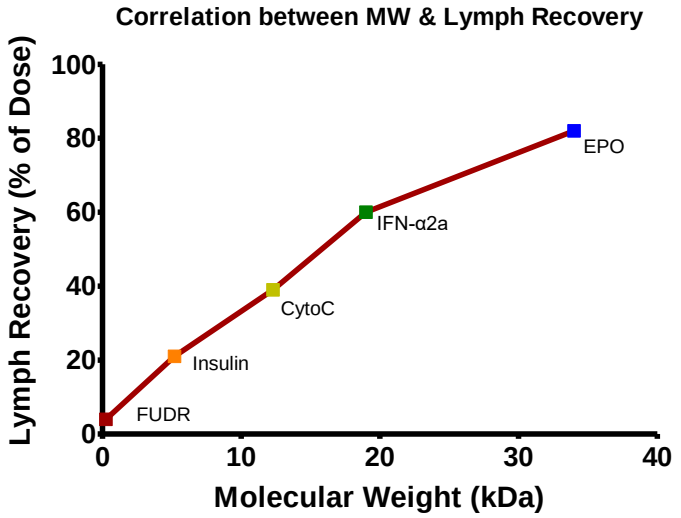
Maria Ciccolella [1], Sara Andreone [1], Jacopo Mancini [1], Paola Sestili [2], Donatella Negri [3], Anna Maria Pacca [4], Maria Teresa D'Urso [4], Daniele Macchia [4], Rossella Canese [5], Ken Pang [6,7,8,9], Thomas SaiYing Ko [6], Yves Decadt [6], Giovanna Schiavoni [1], Fabrizio Mattei [1], Filippo Belardelli [10], Eleonora Aricò [5,*] and Laura Bracci [1,*]

BioLingus' Advantages

After all, sublingual delivery has typically been used to delivery small molecules but not proteins. So, how has BioLingus achieved such systemic protein delivery?

BioLingus has taken advantages of several factors:





Source: Supersaxo, A., Hein, W. R., & Steffen, H. (1990). Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. Pharm Res, 7(2), 167-169.

First, anatomically the sublingual mucosa is very thin and allows ready access to the lymphatics

Secondly, it has previously been established that increasing molecular weight promotes entry into the lymphatic system. In this way, proteins delivered sublingually are intrinsically more likely to enter the lymphatics than small molecules

BioLingus' Advantages

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VOLUME 14 | NOVEMBER 2015

From sewer to saviour — targeting the lymphatic system to promote drug exposure and activity

Natalie L. Trevaskis[1], Lisa M. Kaminskas[1] and Christopher J. H. Porter[1,2]

Abstract | The lymphatic system serves an integral role in fluid homeostasis, lipid metabolism and immune control. In cancer, the lymph nodes that drain solid tumours are a primary site of metastasis, and recent studies have suggested intrinsic links between lymphatic function, lipid deposition, obesity and atherosclerosis. Advances in the current understanding of the role of the lymphatics in pathological change and immunity have driven the recognition that lymph-targeted delivery has the potential to transform disease treatment and vaccination. In addition, the design of lymphatic delivery systems has progressed from simple systems that rely on passive lymphatic access to sophisticated structures that use nanotechnology to mimic endogenous macromolecules and lipid conjugates that 'hitchhike' onto lipid transport processes. Here, we briefly summarize the lymphatic system in health and disease and the varying mechanisms of lymphatic entry and transport, as well as discussing examples of lymphatic delivery that have enhanced therapeutic utility. We also outline future challenges to effective lymph-directed therapy.

Finally, and most importantly, we have developed formulations that help promote delivery of peptides and proteins into the lymphatic system. This work has been done in collaboration with Natalie Trevaskis and Chris Porter at Monash University, who are world leaders in lymphatic delivery.

In summary, BioLingus technology has been designed to promote lymphatic delivery of peptides and proteins, which is ideal for immuno-active compounds such as interferon, given the lymphatic system's key immunological function

Road to Obesity and Diabetes Sublingual

frontiers in Physiology

EDITORIAL
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Editorial: The Role of the Lymphatic System in Lipid and Energy Metabolism, and Immune Homeostasis During Obesity and Diabetes

Vincenza Cifarelli[1], Hong Chen[2] and Joshua P. Scallan[3]*

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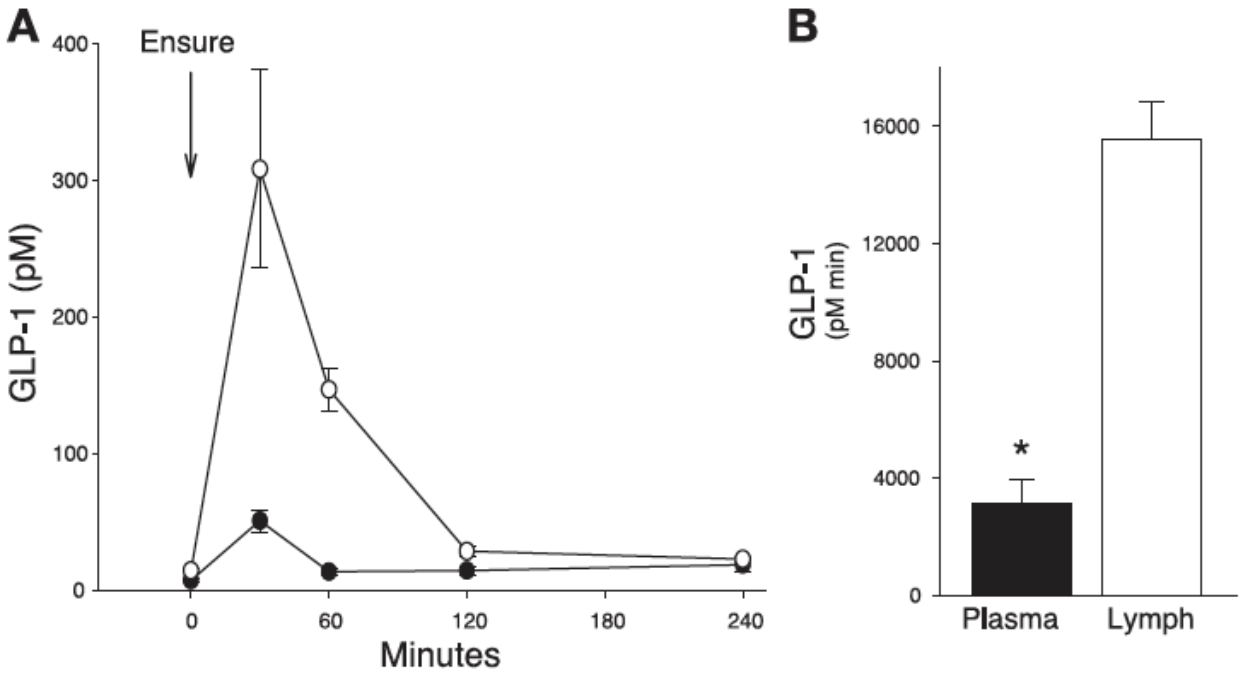
The lymphatic system has also recently been recognized as having key metabolic functions, including in obesity and diabetes.

Road to Obesity and Diabetes Sublingual

For example, a poorly appreciated fact about endogenous GLP-1 is that it mediates its effects via the lymphatic system.

Previous work by the Tso lab (D'Alessio et al, 2007) indicates that endogenous GLP-1 shows a "significantly higher lymph-to-plasma ratio" and is naturally "*concentrated in the lymph compartment*". Based on these findings, the authors suggested that "GLP-1 has specific effects mediated in this [i.e. the lymphatic] compartment".

Fig. 3. *A*: concentrations of glucagon-like peptide 1 (GLP-1) in samples of portal plasma (●) and intestinal lymph (○) taken before and after intragastric Ensure. *B*: area under the curve for GLP-1 in plasma (filled bar) and lymph (open bar). $*P < 0.05$ vs. lymph. Data are presented as means ± SE.



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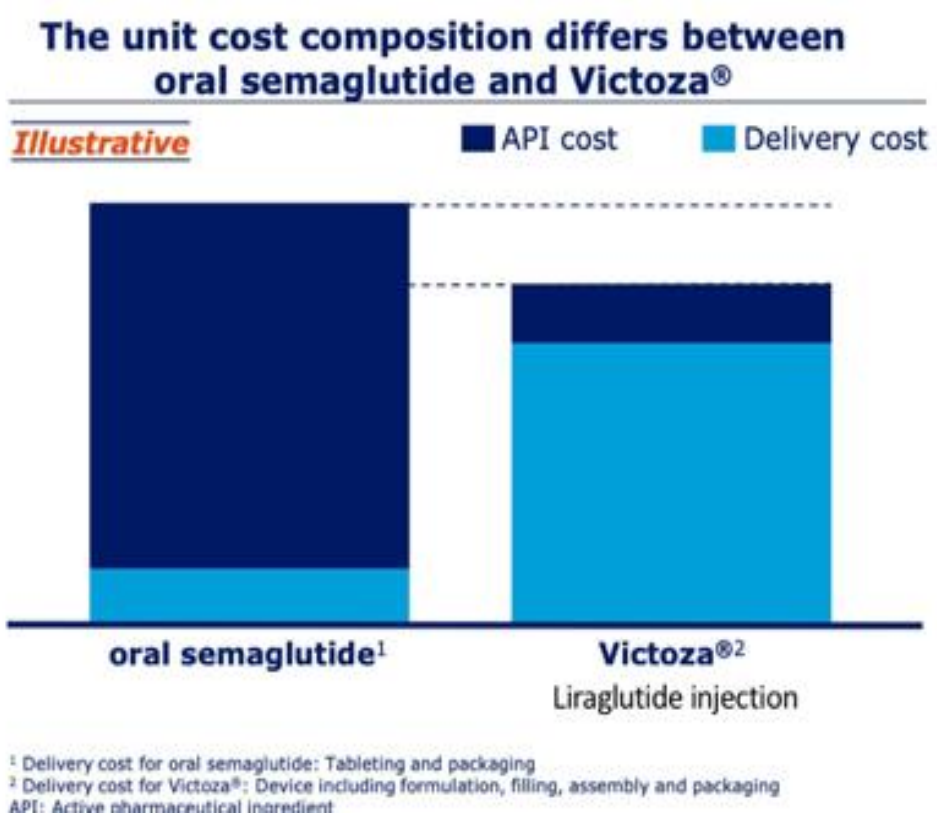
RYBELSUS® semaglutide tablets 7mg | 14mg

Emisphere



With that in mind, BioLingus hypothesized that it could use its technology to more effectively deliver GLP-1 agonists by targeting them to the lymphatic system.

Related to this, it is worth noting that Novo Nordisk's oral delivery technology from Emisphere requires 100x the injectable Semaglutide dose to produce an equivalent effect, which adds considerably to manufacturing costs.

Moreover, this technology does not work with other GLP-1 agonists like liraglutide

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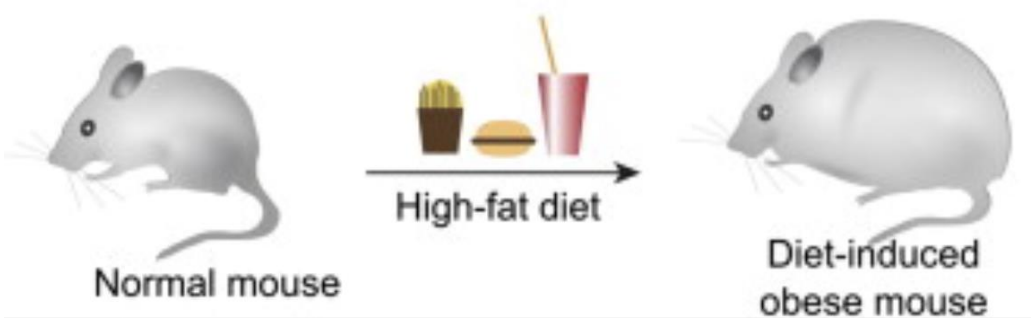
To test its hypothesis, BioLingus initially focused on seeing whether its sublingual (SL) delivery could achieve an equivalent pharmacodynamic effect compared to subcutaneous (SC) injection following glucose challenge in diet-induced obese mice



Glucose tolerance test

Compare sublingual (SL) vs subcutaneous (SC) GLP-1

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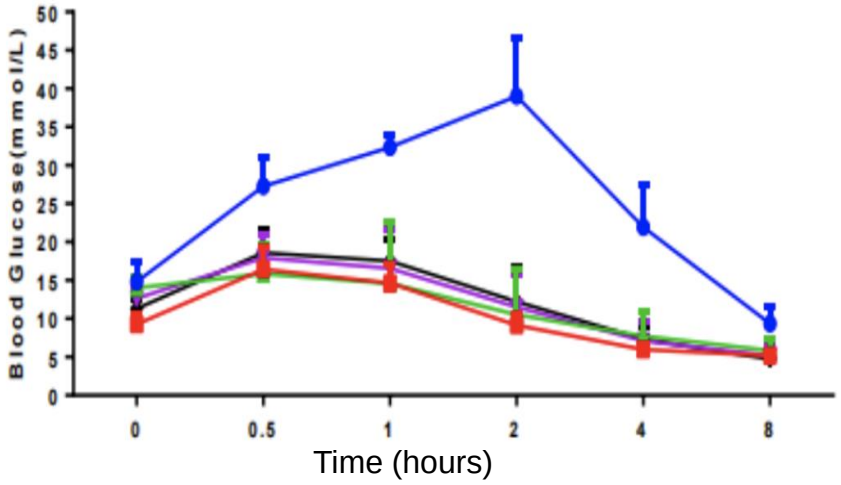
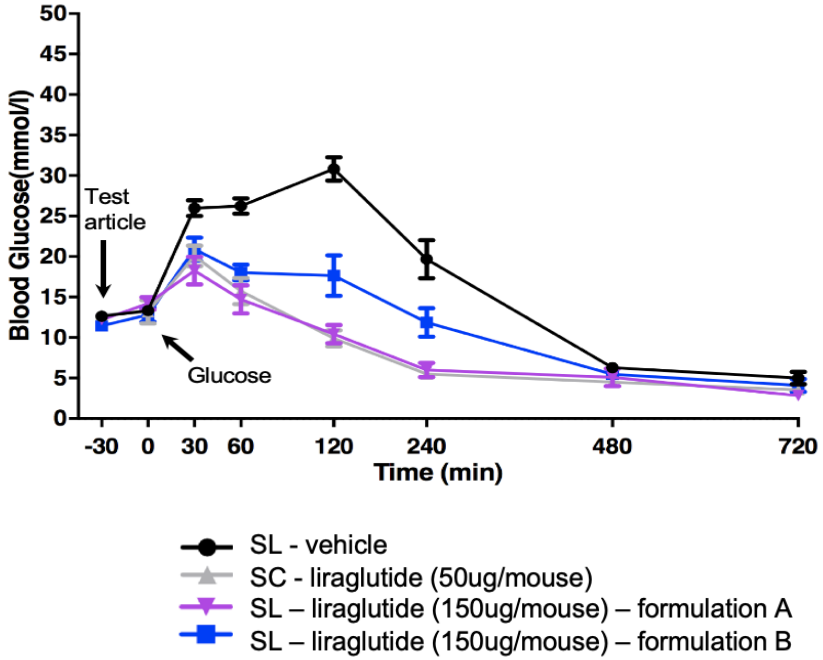
BioLingus' sublingual delivery technology produces an equivalent glucose-lowering effect at 3 - 6x the injectable dose of Semaglutide and works with Liraglutide too.

BioLingus Sublingual Semaglutide



BioLingus Sublingual Liraglutide



Source: BioLingus data provided by independent CRO

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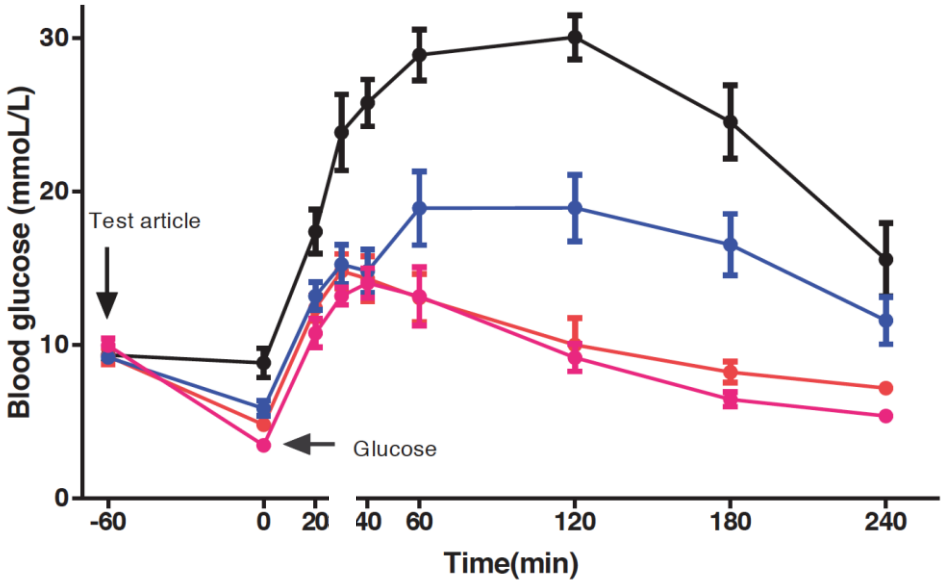
BioLingus' sublingual delivery technology also works with Exenatide, another GLP-1 agonist, and with a dual GLP-1/Insulin product (Insulin+)

BioLingus Sublingual Exenatide

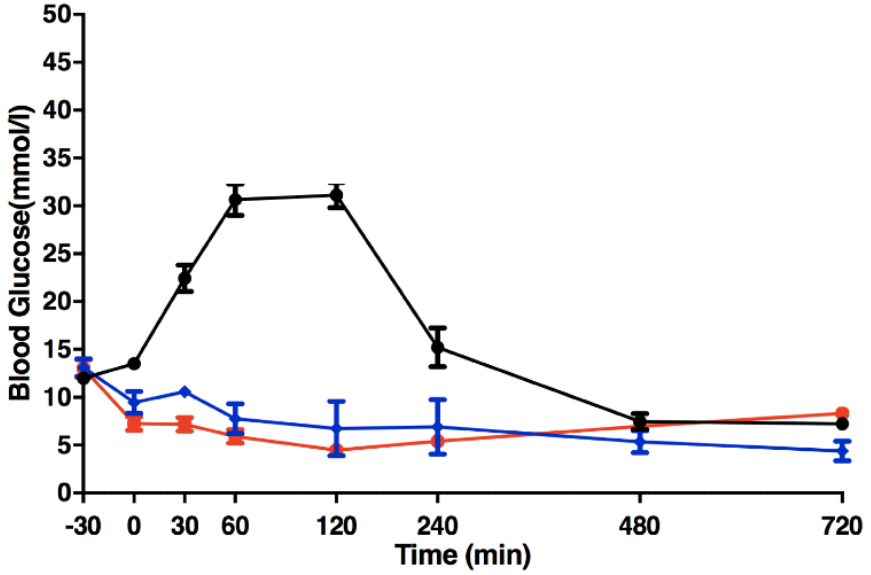
5x injection dose



SL-water only
SL-Exenatide(3ug/mouse)
SL-Exenatide(5ug/mouse)
SC-Exenatide 1ug/mouse

BioLingus Sublingual Insulin+

1 - 2x injection dose



Source: BioLingus data provided by independent CRO

SL-vehicle only
SL-Insulin aspart (1 IU/kg) + Insulin glargine (1 IU/kg) + Exenatide 2ug
SC-Insulin aspart (1 IU/kg) + Insulin glargine (1 IU/kg) + Exenatide 1ug

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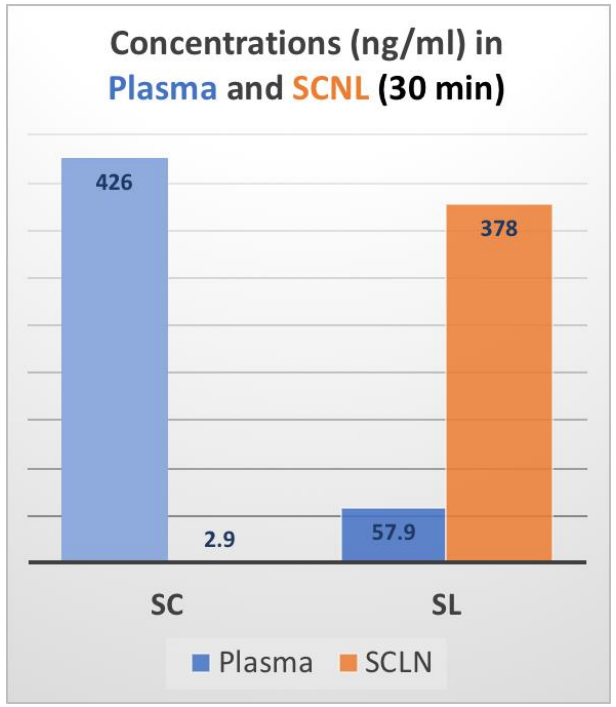
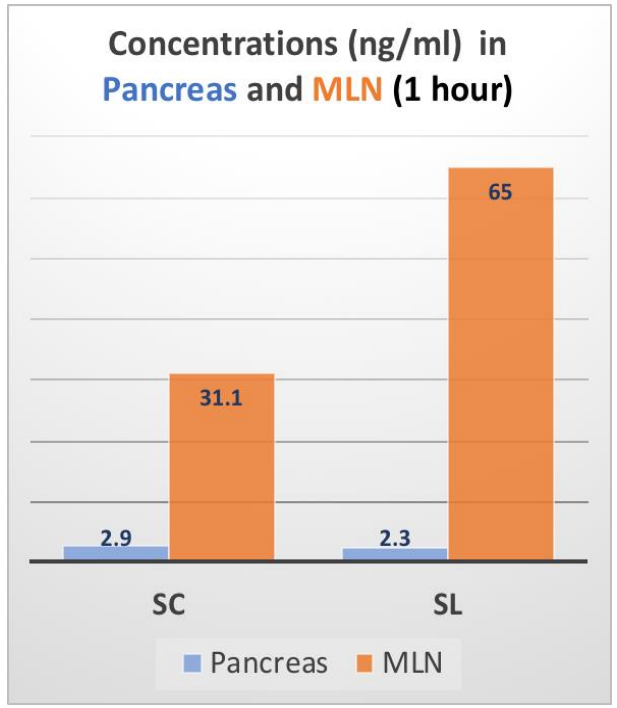
Consistent with its original hypothesis, BioLingus' technology promotes delivery into the local cervical lymphatics and results in equivalent target tissue levels in pancreas and intestinal lymphatics (even though plasma levels are much lower)

In this way, even though the "entry routes" for SC and SL delivery are very different – via the plasma and lymphatics respectively – the target tissue concentrations (e.g. pancreas and intestinal lymphatics) are very similar

Entry route into body



Target tissue: pancreas

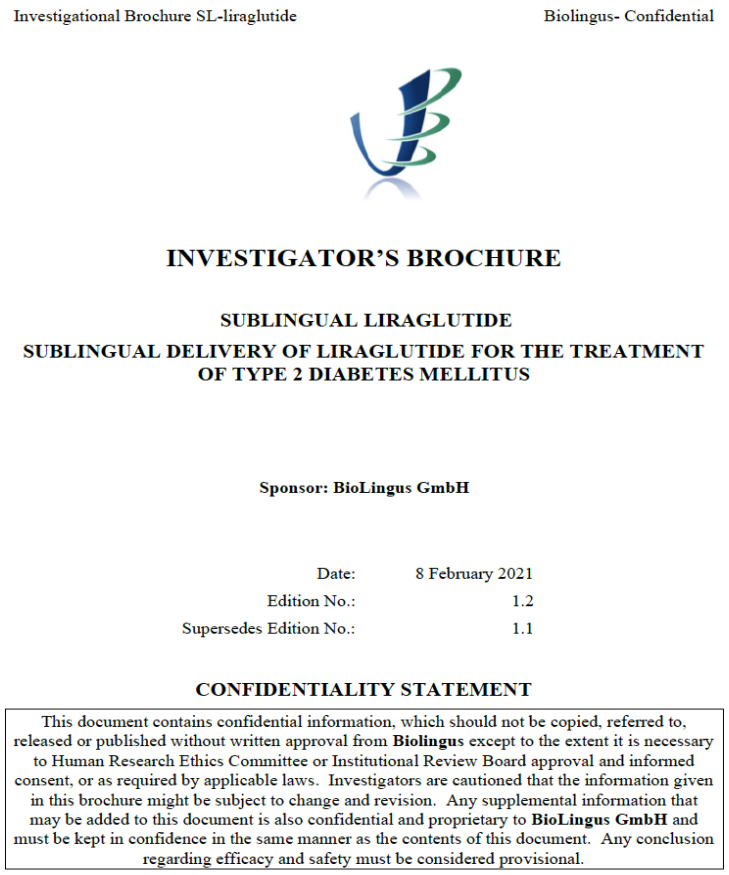


SCLN = Superficial Cervical Lymph Nodes = lymph nodes close to sublingual area; MLN = Mesenteric Lymph Nodes= those lymph nodes closest to pancreas
Source : own experiment conducted at CRO

Road to Obesity and Diabetes Sublingual

The above slides are meant to provide an overview of the relevant scientific background as well as the pertinent PK and PD data related to BioLingus four Pipeline products.

As a further example and for more detailed information, please also refer to the attached Investigator Brochure (IB) for our SL-Liraglutide product which is currently undergoing a phase 1b/2a clinical trial in Hong Kong (https://classic.clinicaltrials.gov/ct2/show/NCT05268237)



Investigational Brochure SL-liraglutide Biolingus- Confidential

INVESTIGATOR'S BROCHURE

SUBLINGUAL LIRAGLUTIDE

SUBLINGUAL DELIVERY OF LIRAGLUTIDE FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Sponsor: BioLingus GmbH

Date: 8 February 2021
Edition No.: 1.2
Supersedes Edition No.: 1.1

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