ACHIEVING THE POTENTIAL OF NASAL DRUG DELIVERY

SNBL is developing its μco™ System for nasal formulation and delivery of small-molecule and protein therapeutics, and intranasal vaccines. In this piece, Shunji Haruta, PhD, Executive Officer, SNBL Ltd, and General Manager, NDS Division, describes the development (including clinical development) of several products in the μco™ System, indicating rapid, effective, safe and well tolerated delivery via the nasal mucosa.

BACKGROUND

Nasal delivery of therapeutics and vaccines has a number of compelling advantages over other routes of administration; namely its non-invasiveness, rapid attainment of therapeutically relevant concentrations to the bloodstream, no first-pass metabolism, and ease of administration.

Viable nasal delivery technologies have the potential to enable drug developers in creating innovative medicines using already approved products by delivering them through new routes of administration. Currently the US FDA offers 505(b)(2) applications to drug developers, which allow the use and reference of approved data from previous NDAs to be applied to the alternatively delivered form of the same drug. An attractive option for pharmaceutical companies, this route to approval both shortens timelines and decreases money required to bring products to market.

As advantageous as the 505(b)(2) pathway is, hindering technical challenges still persist for nasal delivery technologies, the most notable being mucocilliary clearance. Mucocilliary clearance, the continuous flow (clearance) of particles and substances from the nasal cavity into the gastro-intestinal (GI) tract, interferes with rapid and efficient absorption of nasally delivered drugs into the bloodstream. Attempts to mitigate the clearance have generally included the use of nasal mucosal permeation enhancers which unfortunately induce nasal irritation and other local toxicities.[1,2] Additionally, the increase in absorption through the use of enhancers and other marketed nasal delivery technologies still leaves room for the achievement of consistent and high bioavailability.

> "THE WATER-INSOLUBLE, MUCOADHESIVE POWDER CARRIER SIGNIFICANTLY INCREASES RESIDENCE TIME ON THE NASAL MUCOSA, RESULTING IN HIGHER ABSORPTION WITHOUT THE NEED FOR ENHANCERS"

μCO™ SYSTEM

A product of more than ten years in research and development, SNBL's μco™ System represents a major advance in nasal drug delivery. With the premise of eliminating the use of liquids in nasal drug delivery, μco™ System's primary breakthrough came in two areas: first, the highly effective, powder formulation carrier technology; and second, the accompanying easy-to-use nasal device, delivering the powder formulation with high reproducibility. The proprietary system's water-

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insoluble, muco-adhesive powder carrier significantly increases a compound's residence time on the nasal mucosa, therefore resulting in higher absorption without the need for any enhancers. Higher absorption also results in a considerable decrease in variability, another issue plaguing poorly absorbed and traditional nasal delivery systems.[3]

Additionally, the muco-adhesive carrier is water-insoluble and is eventually cleared out of the nasal cavity into the GI tract. The carrier is otherwise inactive in the body, causing no local irritation or safety issues, as observed to date in preclinical and clinical studies.

Finally, perhaps the most compelling advantage of μco™ System is the platform's ability to deliver a wide range of drug compounds, including small molecules and peptides. Its mucosal adhesion qualities also make it a promising technology for locally acting drugs and vaccines.

EXAMPLE APPLICATIONS OF μCO™ SYSTEM

Granisetron

SNBL is currently using the μco™ System to develop a nasally delivered granisetron (TRG). Granisetron is approved as an oral and IV drug (Kytril) indicated for the treatment of cancer patients suffering from chemotherapy-induced nausea and vomiting (CINV). Currently undergoing development in the US, TRG is designed to be the first intranasal, anti-emetic product for patients suffering from CINV.

In a Phase I study, TRG demonstrated complete absorption (100% absolute bioavailability) compared with the marketed granisetron IV injection. Absorption was rapid with maximum concentration (C_{max}) achieved by 20 minutes (70% of C_{max} reached within five minutes) post administration, with low variability observed between patients (Figure 1).

As about half of the granisetron is lost due to first-pass metabolism when given orally and absorbed through the GI tract, the fact that TRG shows 100% bioavailability suggests that nearly all of the granisetron in TRG is being absorbed in the nasal cavity and very little or none is cleared into the GI tract. TRG has been evaluated in 94 human subjects to date and has shown a safety profile comparable to that of Kytril without any observed local nasal irritation.

A preclinical study conducted using SNBL's proprietary and highly effective non-human primate nasal PK evaluation model demonstrated 70% bioavailability with a T_{max} of 30 minutes (Figure 2).

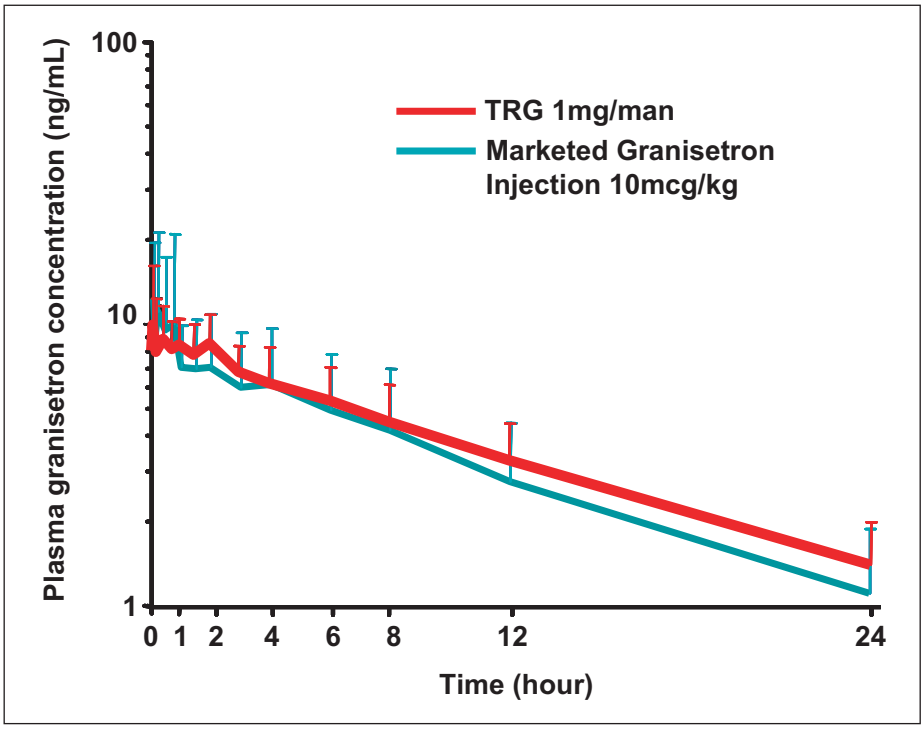

Figure 1: Plasma Granisetron Concentration in Human.

Zolmitriptan

SNBL is also using μco™ System to develop a nasally delivered zolmitriptan (TRZ). Zolmitriptan is currently marketed as Zomig, an oral tablet, an oral disintegrating tablet and a liquid nasal spray, for the treatment of migraine headaches. SNBL is developing TRZ in the US, which promises to be the best-in-class intranasal form of zolmitriptan.

In a Phase I study, TRZ demonstrated higher absorption than the marketed products (both oral and liquid nasal spray) with relative bioavailability of 136% compared with oral tablets, and 182% compared with the nasal spray. More importantly, TRG demonstrated significantly faster absorption than the existing drugs. Specifically, in the first 120 minutes after administration, relative bioavailability was 200% compared with oral tablets and 333% compared with nasal sprays. Maximum concentration was reached within 20 minutes compared with 120 minutes for the marketed

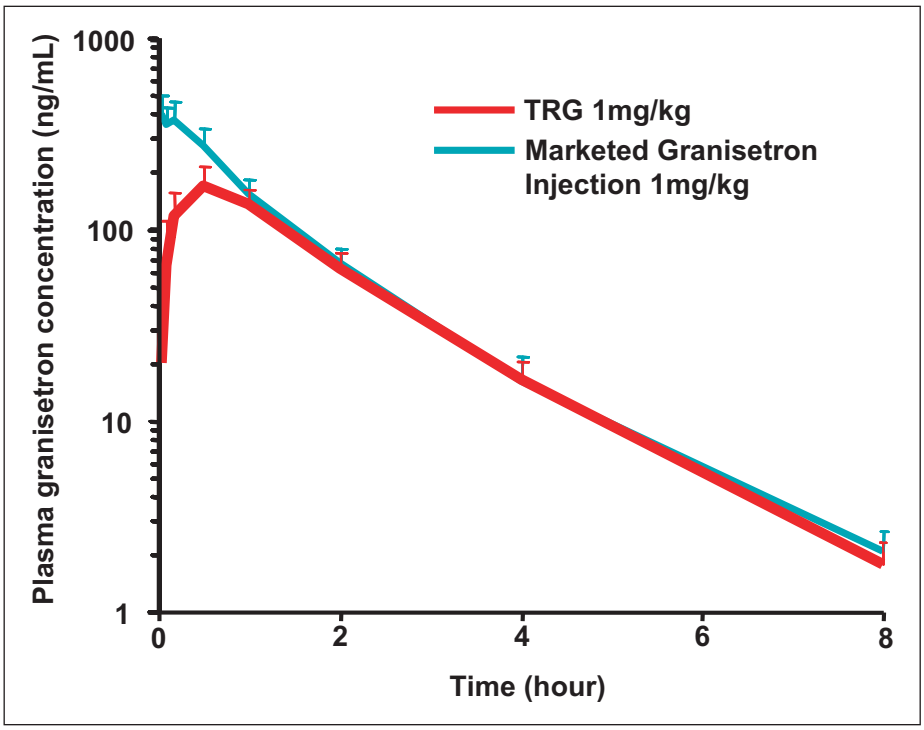

Figure 2: Plasma Granisetron Concentration in Non-Human Primate.

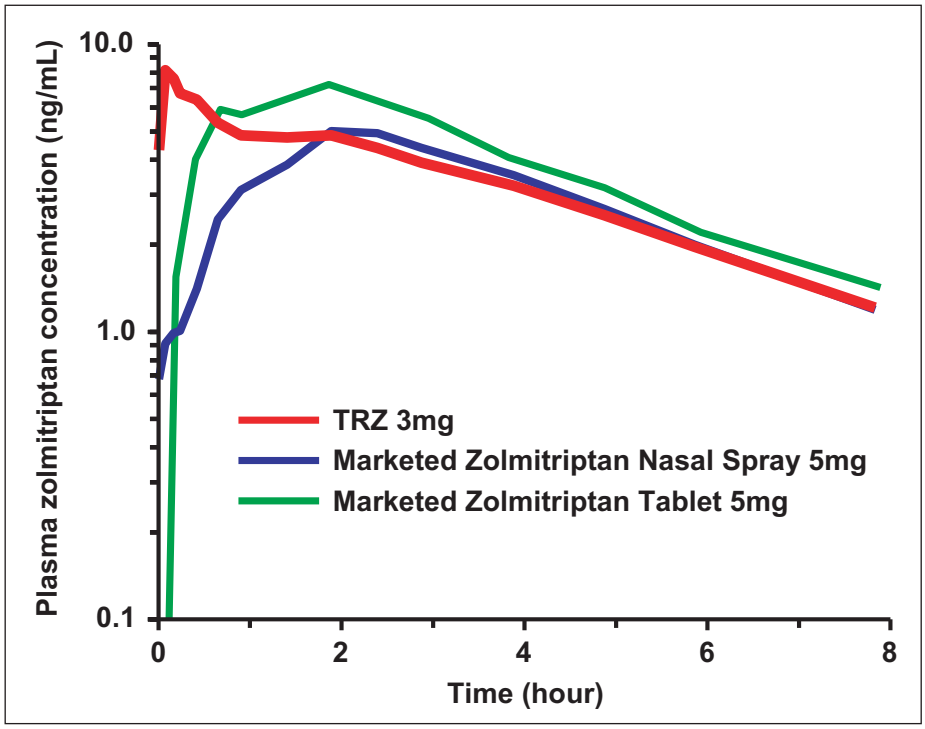

Figure 3: Plasma Zolmitriptan Concentration in Human.

products (see Figure 3). The more rapid PK properties of TRZ strongly suggest the potential for delivering faster headache relief to migraine sufferers.

TRZ is absorbed with greater efficiency and faster kinetics relative to the oral tablet which is, again, consistent with the notion that μco™ System is enabling a large majority of the drug compound to be absorbed through the nasal mucosa into the bloodstream.

Calcitonin

μco™ System has demonstrated high efficiency in delivering peptides into the bloodstream. One example is calcitonin, a 3,431 Dalton peptide indicated for the treatment of osteoporosis and currently available to patients as a liquid nasal spray. In a preclinical study conducted using SNBL's non-human primate PK model, calcitonin delivered by the μco™ System (TRC) showed bioavailability of 17%

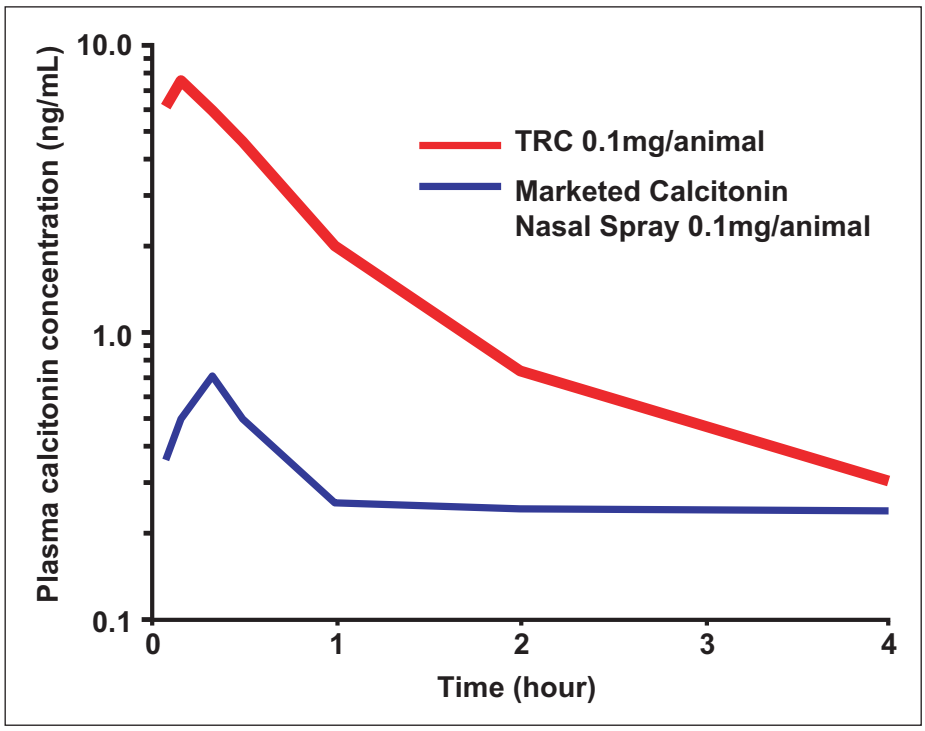

Figure 4: Plasma Calcitonin Concentration in Non-Human Primate.

SNBL'S PREDICTIVE *IN VIVO* PK MODEL

All too often, nasal drug candidates make it into Phase I trials, only to see a large discrepancy in efficacy between the IND trials and first-in-man. This is largely due to the inappropriate choice of animal models. Currently, dog, pig and rodent models are favoured industry-wide for preclinical testing of nasal drugs. These models, however, are not highly predictive of PK in humans. Due to the large surface area relative to bodyweight and significant differences in the nasal anatomy,[4,5] PK evaluation in dogs, pigs and rodents may be significantly over-estimated, leading to disappointing clinical trial results and large amounts of wasted R&D money. Non-human primates are truly the best model for preclinical testing of efficacy and safety because the nasal cavity structure is far more similar to that of humans than other test models.

SNBL has developed a non-human primate nasal administration model for these reasons. But in order to create a better predictive model, SNBL has also engineered and validated a nasal administration device which monitors the breathing cycle of the animal and automatically synchronises the administration with the inhalation phase. SNBL's model also enables administration in an unanaesthesised state.

This highly effective and predictive model has important advantages. First, due to an unanaesthetised animal and full administration during the exact appropriate phase in the breathing cycle, results are likely to be more similar to those expected in humans because the model more closely mimics human self-administration of a nasal drug. Secondly, variability is greatly reduced, necessitating as little as three animals per study to obtain reliable results.

As used in the development of SNBL's own nasal products, this model enables more informed optimisation of the formulation and business decision making at a very early stage in development before committing resources to more costly and time-consuming GLP or clinical studies.

compared with IV bolus injection, whereas the marketed liquid nasal spray exhibited only 4% bioavailability compared with IV injection (Figure 4).

SUMMARY

As demonstrated by the examples described above, μco™ System rapidly and effectively delivers drugs (both small molecules and peptides) via the nasal cavity into the bloodstream with consistently high efficiency. Notably, observations in clinical trials to date strongly suggest that μco™ System is safe with very high tolerability.

Although this article has only described applications for delivering drugs systemically, μco™ System also represents an effective platform for delivering vaccines locally to the nasal mucosa. Due to the muco-adhesive carrier's prolonged retention time, the platform enables efficient delivery of vaccines to the nasal mucosa, resulting in the generation of an effective mucosal immune response. Given these promising properties, SNBL is using μco™ System to actively pursue the development of a number of nasally-delivered vaccines.

In summary, μco™ System is an effective platform to deliver drugs systemically via the nasal cavity, with promising effects for locally acting drugs as well as nasal vaccines. μco™ System represents a significant advance in the field towards delivering on the long-held promises of nasal delivery. SNBL is using μco™ System to develop best- and/or first-in-class therapeutics for opportunities of significant clinical unmet needs. SNBL is also actively partnering with leading pharmaceutical companies to use this platform to enable effective nasal delivery of their internally developed therapeutics and vaccines.

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Figure 5: Prefilled Single-Use Device.

Figure 6: Capsule-Loading Multiple Use Device.

SNBL'S μCO™ SYSTEM

μco™ System consists of two proprietary and complimentary technologies. The first is a GRAS muco-adhesive carrier which is entirely water-insoluble. The carrier effectively prolongs the retention time, allowing the API time to solubilise, permeate the membrane and transfer directly into the bloodstream. The carrier requires no absorption enhancers and causes no irritation or damage to the mucosal membrane; preclinical and clinical studies with μco™ System carrier have confirmed no irritation or damage. The water-insoluble carrier is eventually cleared out of the nasal cavity by the mucocilliary clearance into the GI tract; it has no other effects in the body.

The second of the complimentary technologies is a line of in-house designed nasal devices, consisting of a single-use device (Figure 5), and a multiple-use device (Figure 6). These devices provide excellent patient control over treatment as they are easy-to-use and portable, and they are designed to provide consistent and complete delivery (Figure 7) for a wide variety of patient types. The single-use device is preloaded with drug formulation and disposed of after use. The multiple use device accepts encapsulated formulations with negligible residue build-up even after high usage.

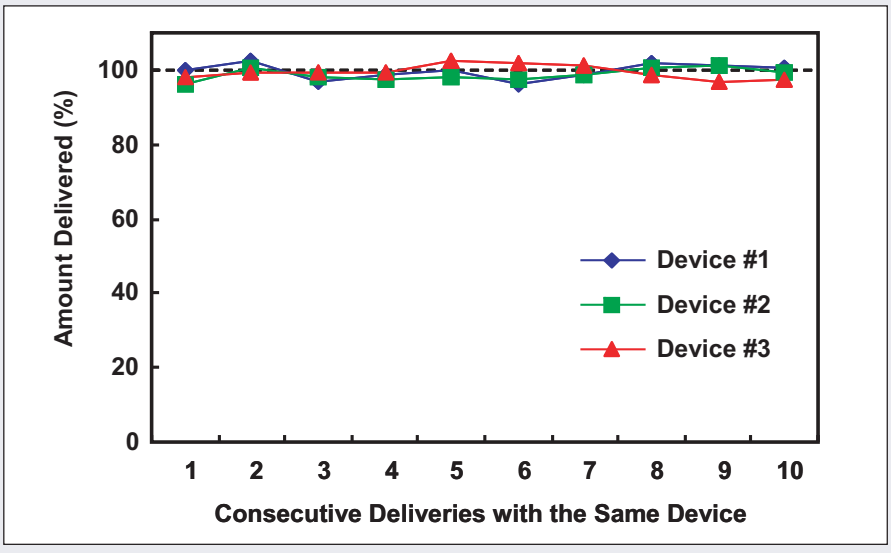

Figure 7: Amount of Formulation Delivered over Multiple Uses.

romeo & juliet

summertime & flip-flops

thunder & lightning

chicken noodle soup & crackers

batman & robin

peanut butter & jelly

movies & popcorn

campfires & scary stories

salt & pepper

baseball & hot-dogs

ken & barbie

tom & jerry

nuts & bolts

hot days & lemonade

rock & roll

wine & cheese

coffee & biscotti

warm cookies & cold milk

yin & yang

lock & key

good friends & belly laughs

golden retrievers & frisbees

μco™ System & (your API)

Great things come in pairs. Have you paired yet?

Impressive preclinical & clinical efficacy
Proprietary powder carrier & devices
Excellent predictive study model
Choice knowledge & know-how

Undeniably better nasal drug delivery
The benefits for your drug product are endless

Find out why our pair works:
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