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**Results of Phase I Clinical Trial**  
**for Intranasal Granisetron Formulation (First Report)**

Translational Research, Ltd. (TRL), a 100% subsidiary company of Shin Nippon Biomedical Laboratories, Ltd. (SNBL), is developing an intranasally delivered form of granisetron (TRG), a drug with anti-emetic effects, in the US. The results of the Phase I Clinical Trial were successfully obtained.

[Summary]

The safety and pharmacokinetics of TRG in healthy volunteers were evaluated by the single intranasal administration of each of the following three doses of TRG: 0.5mg, 1.0mg and 2mg, to enable comparison with a single intravenous dose of granisetron at 10µg/kg. The results were as follows:

1. **The absorption of TRG through the nasal mucosa was dose dependent** across all delivered doses.
2. The blood concentration profile of granisetron after the administration of **1.0 mg TRG was almost the same as that after the intravenous administration of 10 µg/kg of granisetron.**
3. **The bioavailability of 1.0 mg TRG was approximately 90%**, which is higher than that of the granisetron oral tablets (bioavailability: 60%) currently available in the market.
4. **The excellent safety profile of TRG was demonstrated.** No irritation was observed in any subjects upon thorough examination by otolaryngologists. Also, clinically,

neither symptoms nor adverse events that signified local irritation to the nasal mucosa were observed. Furthermore, clinical laboratory tests showed no abnormal changes during the dosing period.

### **[Description]**

As noted in the press release of November 27, 2007, the US Food and Drug Administration (FDA) reviewed and cleared the Investigational New Drug (IND) file of TRG, and TRL conducted a Phase I clinical trial of TRG in healthy volunteers. Below are the details of the trial.

During the treatment of cancer by chemotherapy and radiation therapy, cancer patients often suffer side effects such as severe nausea and vomiting. Granisetron has the ability to prevent these side effects and is already available in the market in the form of oral tablets and intravenous injections. However, correct dosing of an oral tablet can be difficult, if patients are suffering from nausea or vomiting or if the patient's swallowing capability is hindered. Also, injections can be difficult, as they are invasive to patients and need to be performed by either a doctor or a registered nurse. Therefore, the existing oral tablet and injectable forms of granisetron do not fully meet the unmet needs of patients and medical staff, and thereby the development of a new delivery method that is easier and more precise is desired. TRG, under development by TRL, allows patients to self-dose, precisely and easily, even when swallowing is difficult. Because of these characteristics, TRG is greatly awaited in the clinics and hospitals.

The Phase I clinical trial confirmed dose-dependently the consistent and reliable absorption of granisetron through the nasal mucosa at all doses tested (0.5 mg, 1.0 mg, and 2.0 mg of granisetron), as shown in Figure 1 and Figure 2.

Also, the dose of 1.0 mg of TRG is almost the same as the recommended dose of the intravenous injection of granisetron, which is 10 µg/kg., after conversion of units using the average weight of the subjects, which was about 80 kg. The blood concentration profile after administration of 1.0 mg TRG is very similar to that of 10 µg/kg intravenous injection, as shown in Figure 3.

The pharmacokinetic parameters of orally administered granisetron (Kytril® 2 mg tablets) are reported as follows (Publication 1):  $T_{max}^{*1}$ ;  $2.05 \pm 0.69$  (hr),  $C_{max}^{*2}$ ;  $9.05 \pm 3.52$  (ng/mL),  $T_{1/2}^{*3}$ ;  $5.29 \pm 3.34$  (hr),  $AUC^{*4}$ ;  $79.61 \pm 50.00$  (ng · hr/mL). The bioavailability<sup>\*5</sup> of oral granisetron has been reported to be around 60% (Publication 2). On the other hand, the pharmacokinetic parameters of 1.0 mg TRG are as follows:  $T_{max}$ ;  $0.36 \pm 0.34$  (hr),  $C_{max}$ ;  $13.37 \pm 5.87$  (ng/mL),  $T_{1/2}$ ;  $9.55 \pm 0.80$  (hr),  $AUC_{last}$ ;  $104.88 \pm 32.82$  (ng · hr/mL). The bioavailability of TRG was found to be around 90%, which is clearly higher than that of the oral tablets. Additionally, the blood concentration of TRG reaches 45% of the  $C_{max}$  5 minutes after dosing. Therefore, it is possible to expect that TRG will have onset and efficacy comparable to that

of intravenously injected granisetron.

The excellent safety profile of TRG was confirmed. No irritation was observed in any subjects upon thorough examination by otolaryngologists. Also clinically, there were neither symptoms nor adverse events that signified local irritation to the nasal mucosa. Furthermore, clinical laboratory tests showed no abnormal changes during the dosing period.

During the Phase I trial, TRG was administered into the nasal cavity using an intranasal drug delivery device, Fit-lizer®, developed by Bioactis, Ltd., an SNBL subsidiary company. Fit-lizer® is a high performance, easy-to-use drug delivery device that is able to deliver consistently more than 95% of the loaded formulation in one actuation.

Currently, TRL has multiple intranasal drugs in the development pipeline, other than granisetron, including analgesics (morphine and fentanyl), a drug for migraine, and insulin. It is highly probable that the same novel formulation technology developed by TRL can be applied to the other pipeline candidates.

The effect of this new venture on the earnings of SNBL's current term is minimal. However, using the results and findings of this clinical trial, we will pursue opportunities to license-out the technology to pharmaceutical companies or establish a joint-development relationship. Thus, we will continue to strive to increase the corporate value of the SNBL Group.

#### **[Footnote]**

\*1  $T_{max}$ : Time after dosing the drug, when the drug concentration in the blood reaches the maximum.

\*2  $C_{max}$ : Maximum drug concentration in the blood reached after dosing.

\*3  $T_{1/2}$ : Time it takes for the drug concentration to become half of the original value.

\*4 AUC: Area Under the blood concentration time Curve of blood concentration vs time graph. This characterizes the total amount of drug that was absorbed by the body.

\*5 Bioavailability: This characterizes the percentage of drug delivered that exhibits pharmacological action in the body after absorption in the blood stream.

#### **[Publication]**

Publication 1: Shinobu Kudo, et al; Japanese Pharmacology & Therapeutics, 24:1529, 1996

Publication 2: F. Hoffmann-La Roche Ltd., MoH Approved Prescribing Information of Kytril®

[Figures]

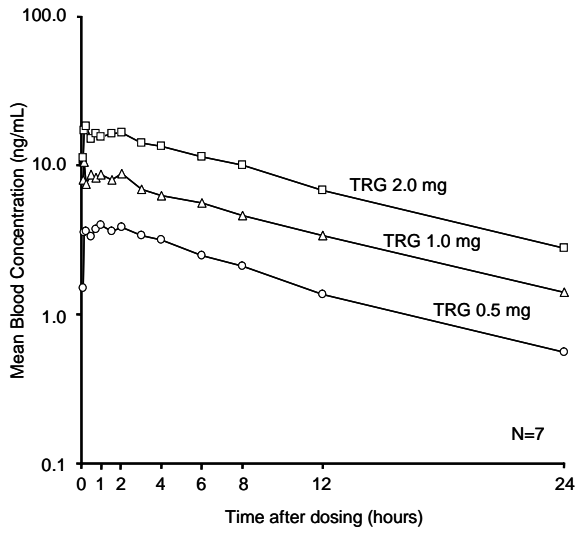


Figure 1: Blood concentration profile of granisetron after TRG administration

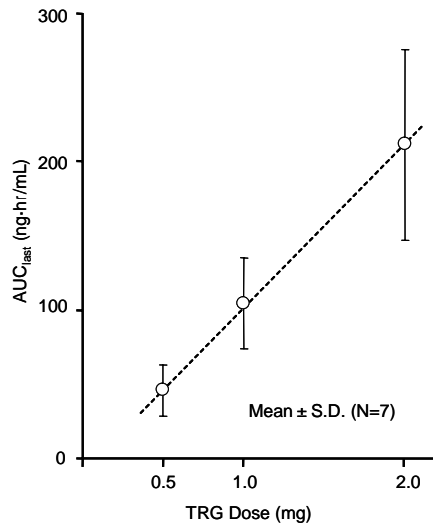


Figure 2: Relationship between TRG dose and AUC

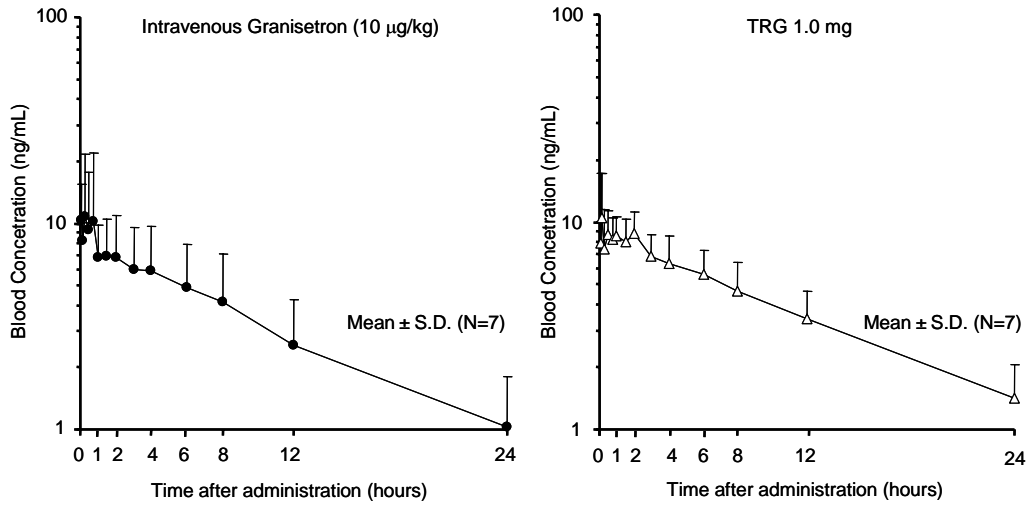


Figure 3: Comparison of blood concentrations of granisetron after administration of intravenous granisetron and TRG