A first-in-human study of the anti-inflammatory profibrinolytic TMS-007, an SMTP family triprenyl phenol

Takashi Moritoyo¹, Naoko Nishimura², Keiko Hasegawa², Ishii Shinya¹, Kenji Kirihara¹, Munenori Takata¹, Akiko Kishi-Svensson¹, Yumi Umeda-Kaneyama¹, Shuichi Kawarasaki¹, Ryoko Ihara¹, Chie Sakanaka¹, Yurie Wakabayashi¹, Kuniyasu Niizuma³, Teiji Tominaga³, Tsutomu Yamazaki¹, and Keiji Hasumi⁴

¹The University of Tokyo Hospital
²TMS Co., Ltd.
³Tohoku University Graduate School of Medicine
⁴Tokyo University of Agriculture and Technology

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Abstract

Background: TMS-007, an SMTP family member, modulates plasminogen conformation and enhances plasminogen-fibrin binding, leading to promotion of endogenous fibrinolysis. Its anti-inflammatory action mediated by soluble epoxide hydrolase inhibition contributes to the efficacy. Evidence suggests that TMS-007 can effectively treat experimental thrombotic and embolic strokes with a wide time window while reducing hemorrhagic transformation. Aims: To evaluate the safety, pharmacokinetics, and pharmacodynamics of TMS-007 in healthy volunteers. Methods: A randomized, placebo-controlled, double blind, dose-escalation study, administered as a single intravenous infusion of TMS-007 in cohorts of healthy male Japanese subjects. There were 6 cohorts planned, but 5 were completed. In each cohort (n = 8), individuals were randomized to receive one of 5 doses of TMS-007 (3, 15, 60, 180, or 360 mg; n = 6) or placebo (n = 2). Results: TMS-007 was generally well-tolerated, and no serious adverse events attributed to the drug. A linear dose-dependency was observed for plasma TMS-007 levels. No symptoms of bleeding were observed in brain MRI analysis, and no bleeding-related responses in laboratory testing were found. The plasma levels of the coagulation factor fibrinogen and the anti-fibrinolysis factor α2-antiplasmin levels were unchanged after the TMS-007 dosing. A slight increase in the plasma level of plasmin-α2-antiplasmin complex, an index of plasmin formation, was observed in some subjects who received 360 mg of TMS-007 (6 mg kg⁻¹). Conclusions: TMS-007 is generally well-tolerated and exhibits favorable pharmacokinetic profiles that warrant further clinical development.

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Cohort 1
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2

Cohort 2
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2

Cohort 3
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2

Cohort 4
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2

Cohort 5
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2

Excluded
placebo, n = 1

Full analysis set,
 n = 40

Per-protocol analysis set,
 n = 39

Figure 1
Figure 2
Figure 3
Figure 4