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

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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 ?2-antiplasmin levels were unchanged after the TMS-007 dosing. A slight increase in the plasma level of plasmin-α_2-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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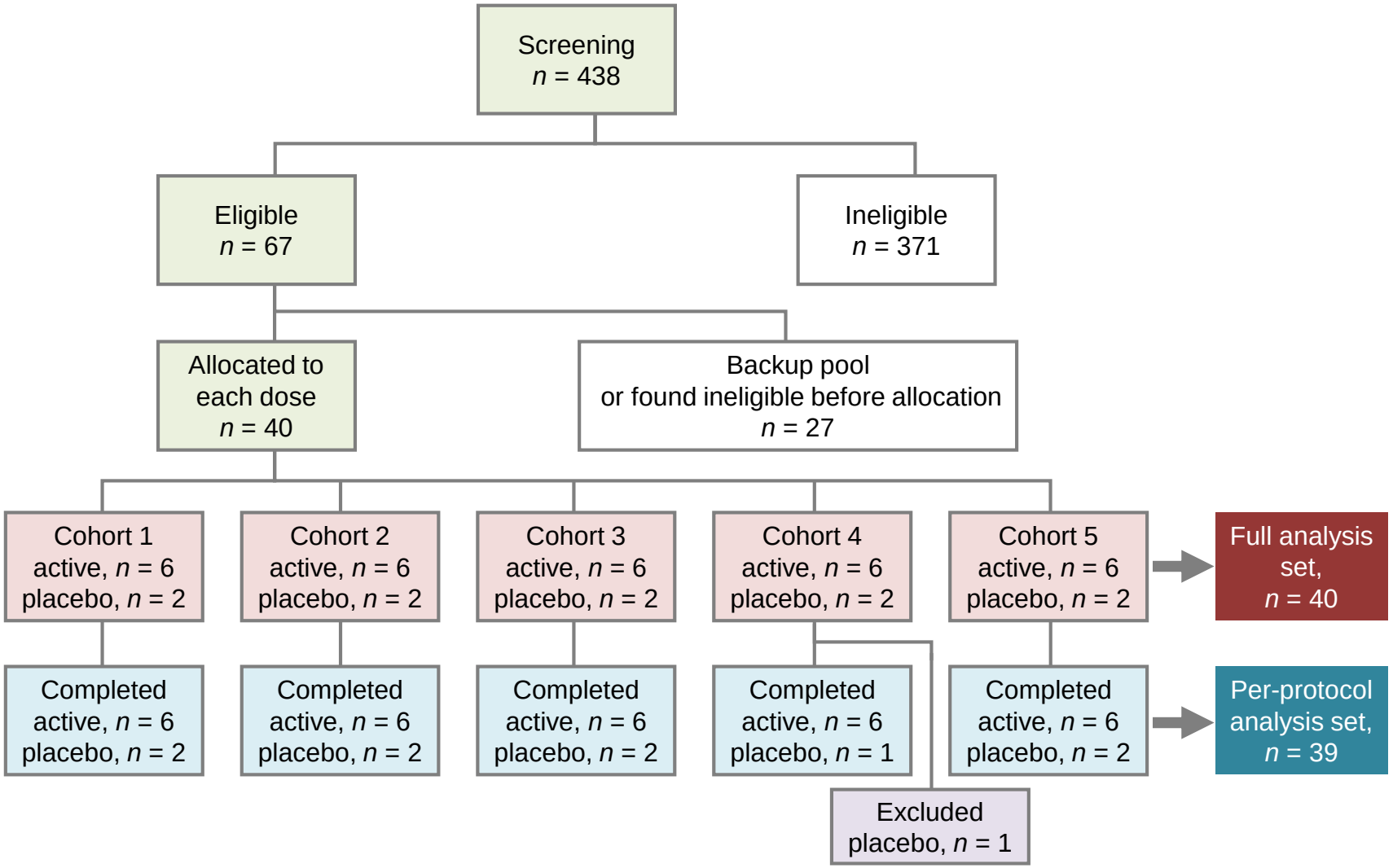
Screening
n = 438
Eligible
n = 67
Ineligible
n = 371
Allocated to each dose
n = 40
Backup pool
or found ineligible before allocation
n = 27
Cohort 1
active, n = 6
placebo, n = 2
Cohort 2
active, n = 6
placebo, n = 2
Cohort 3
active, n = 6
placebo, n = 2
Cohort 4
active, n = 6
placebo, n = 2
Cohort 5
active, n = 6
placebo, n = 2
Full analysis set,
n = 40
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 1
Completed
active, n = 6
placebo, n = 2
Per-protocol analysis set,
n = 39
Excluded
placebo, n = 1

Figure 1

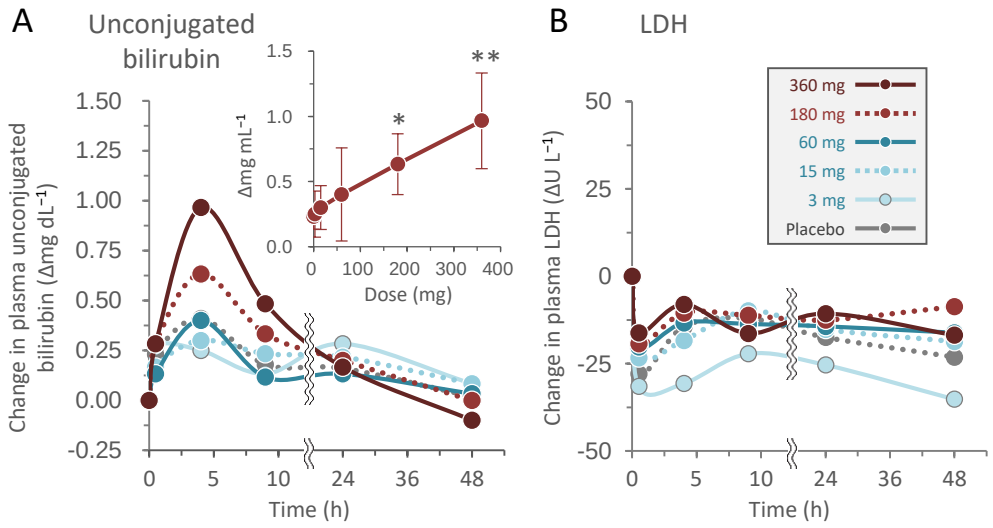
A
Unconjugated bilirubin
Change in plasma unconjugated bilirubin (Δmg dL⁻¹)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
0
5
10
24
36
48
Time (h)
Δmg mL⁻¹
1.5
1.0
0.5
0.0
*
**
0
100
200
300
400
Dose (mg)
B
LDH
Change in plasma LDH (ΔU L⁻¹)
50
25
0
-25
-50
0
5
10
24
36
48
Time (h)
360 mg
180 mg
60 mg
15 mg
3 mg
Placebo

Figure 2

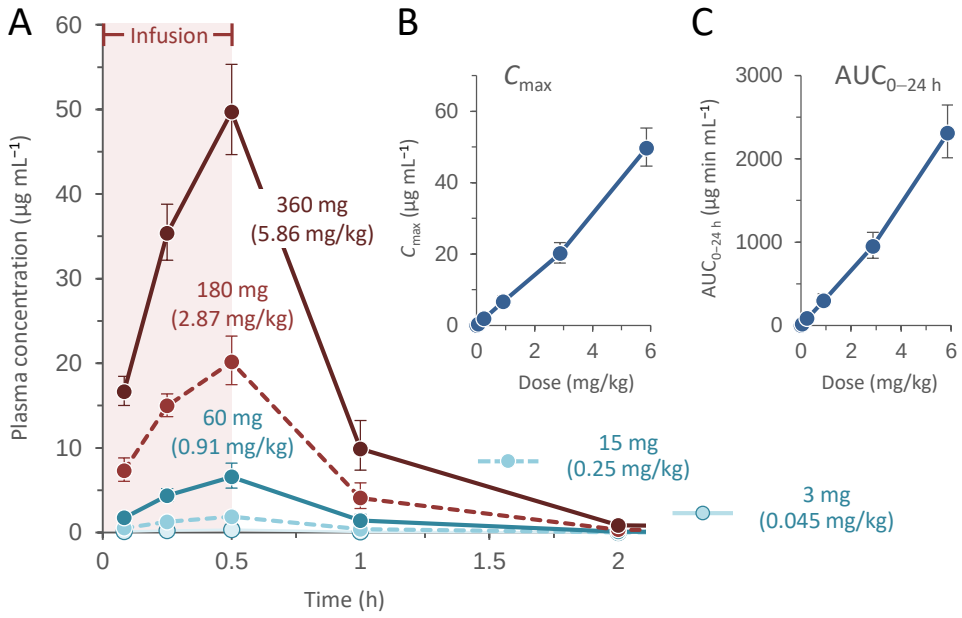
A
B
C
Infusion
360 mg
(5.86 mg/kg)
180 mg
(2.87 mg/kg)
60 mg
(0.91 mg/kg)
15 mg
(0.25 mg/kg)
3 mg
(0.045 mg/kg)
Plasma concentration (µg mL⁻¹)
Time (h)
Cmax
Cmax (µg mL⁻¹)
Dose (mg/kg)
AUC0–24 h
AUC0–24 h (µg min mL⁻¹)
Dose (mg/kg)

Figure 3

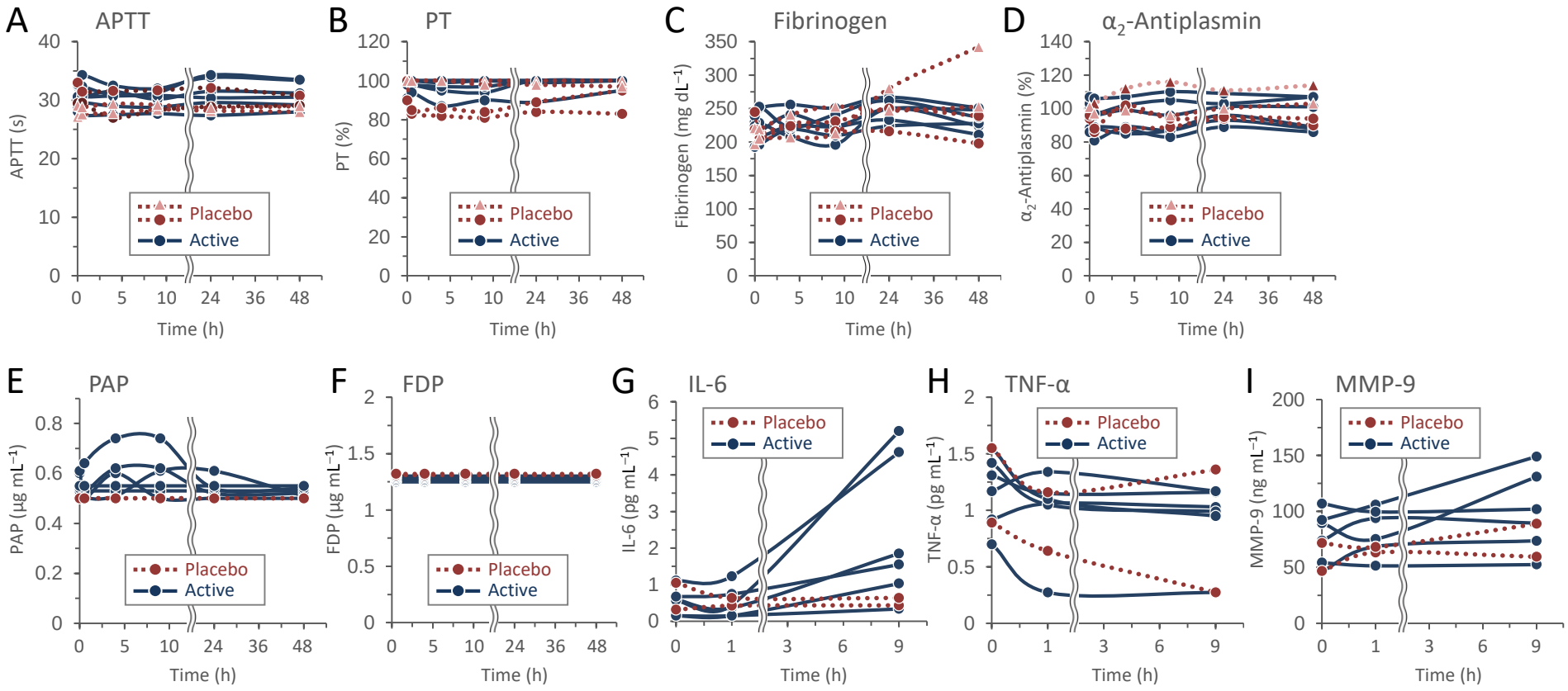
A
APTT
APTT (s)
Time (h)
B
PT
PT (%)
Time (h)
C
Fibrinogen
Fibrinogen (mg dL⁻¹)
Time (h)
D
α2-Antiplasmin
α2-Antiplasmin (%)
Time (h)
E
PAP
PAP (μg mL⁻¹)
Time (h)
F
FDP
FDP (μg mL⁻¹)
Time (h)
G
IL-6
IL-6 (pg mL⁻¹)
Time (h)
H
TNF-α
TNF-α (pg mL⁻¹)
Time (h)
I
MMP-9
MMP-9 (ng mL⁻¹)
Time (h)
Placebo
Active

Figure 4