

## K10

### **Proof of concept for the anti-von Willebrand factor aptamer ARC1779 in a patient with familial thrombotic thrombocytopenic purpura (TTP)**

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#### **Background**

Thrombotic thrombocytopenic purpura (TTP) has a high morbidity and mortality rate despite current standard therapy comprising plasma exchange (PEX). Aim of this prospective clinical trial was to test the safety and efficacy of the anti-von Willebrand factor aptamer ARC1779 in a patient with familial TTP.

#### **Methods**

This was a prospective open label trial with three periods. A bolus-primed continuous intravenous infusions of ARC1779 (0.002 mg/kg/min) was given in period I for 24 hours. In the second period, ARC1779 (50 mg) was administered s.c. on 7 subsequent days, afterwards tapered twice (25 mg on day 8 and 12.5 mg on day 9). Finally, the patient received a bolus-primed continuous infusion of 0.004 mg/kg ARC1779 for 48 hours and 0.006 mg/kg up to a total of 72 hours. ARC1779 concentrations were quantified by a high-performance liquid chromatography/ultraviolet assay, the inhibitory effect of ARC1779 on vWF activity was evaluated with an ELISA kit (REAADS vWF Activity ELISA Test Kit, Corgenix Inc., Westminster, CO, USA), and platelet function was assessed with the platelet function analyzer (PFA-100).

#### **Results**

ARC1779 was well tolerated without any evidence of bleeding. Median steady-state ARC1779 concentrations were approximately 10 µg/mL (24h i.v.) in period I, morning trough values were 0.6 µg/mL (s.c.) in period II, and 64 µg/mL (high dose i.v.) in period III. Continuous infusion of the high doses inhibited the collagen binding site of the vWF A1 domain by >95%, the lower i.v. dose by 85%, and s.c. injected ARC1779 decreased vWF activity to 57% of normal activity. Inhibition of vWF activity was mirrored by maximal prolongation of collagen/ADP closure times when the drug was infused i.v., but not when ARC1779 was injected subcutaneously. Hence, s.c. injected ARC1779 did not reach therapeutically effective plasma concentrations and therefore could not prevent the periodic drop in platelet counts observed every month in this patient. In striking contrast, ARC1779 raised the platelet count by 46% when given 24h i.v., or even by 106% when given for 72h intravenously.

#### **Conclusions**

This cross-over trial supports the concept that ARC1779 concentration-dependently restores platelet counts, and interferes with the disease process in familial TTP.