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Stroke Recurrence and Mortality with Recombinant Tissue Kallikrein Protein in the ReMEDy1 Phase 2 Trial

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Introduction

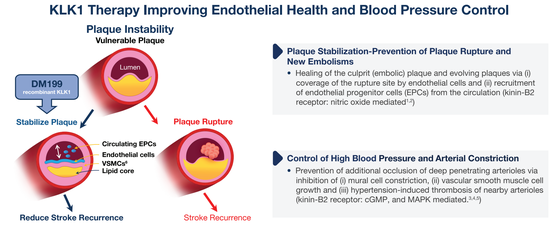
Recurrent ischemic strokes account for 25% of the 800,000 strokes that occur annually in the United States (Oza et al, 2017), and the rate of stroke recurrence has remained steady over the last 15 years (Oza et al, 2017; Flach et al, 2020). A large proportion of recurrent strokes occur during the first 30 days after the index stroke (Ay et al, 2010; Mohan et al, 2011).

Prevention of early recurrent ischemic strokes are critical because they lead to severe consequences including longer duration of hospitalization and increased neurologic disability and death. The fatality rate of early recurrent strokes is almost twice that of first-ever strokes at 30 days (Hardie et al, 2004). Therefore, there is a need for developing new therapies to reduce stroke recurrence.

Human tissue kallikrein-1 (KLK1) is a serine protease that plays a critical role in regulation of microcirculation, blood pressure and blood flow via release of bradykinin from low molecular weight kininogen (Regoli and Gobeil, 2016; Naicker et al, 1999; Perez-Blanco et al, 1997). KLK1 regulates local blood flow and vasodilation and mitigates inflammation and oxidative stress (Alhenc-Gelas et al, 2019; Devetzi et al, 2018; Tschope et al, 2002; Mitchell et al, 2008).

Meta-analyses have indicated that treatment with urinary-derived KLK1 (uKLK1) is associated with improved neurological outcomes and a reduction in death and dependency at 3 months among patients with AIS (Huang et al, 2020; Zhang et al, 2012). Furthermore, “Lower plasma KLK1 levels are independently associated with first-ever stroke and are an independent predictor of recurrence after an initial stroke.” (Zhang et al, Ann Neurol 2011).

Figure 1. Rationale for KLK1 Therapy to Reduce Stroke Recurrence by Stabilizing Plaque



1. Kraenkel et al. *Circulation*, 2013;127:594–603; 2. Spinetti et al. *Circulation Research*. 2011;108:284–93; 3. Yemisci et al. *Nat Med*. 2009 Sep;15(9):1031-7; 4. Lan et al. *Int J Stroke* 2014 Jun;9(4):533-5; 5. Emanueli et al. *Arterioscler Thromb Vasc Biol* 2000, Nov;20(11):2379-85; 6. Vascular Smooth Muscle Cells (VSMC)

DM199 is a recombinant form of KLK1 that can be administered by subcutaneous (SC) injection once every 3 days versus daily intravenous (IV) infusions required for the urinary form (uKLK1) used for treating AIS in China (Alexander-Curtis et al, 2019; Nakayama et al, 1996). Data from a Phase 1 study in healthy volunteers indicated that DM199 was generally safe and well tolerated at all dose levels following both IV and SC routes of administration (Alexander-Curtis et al, 2017). Pharmacokinetic data also confirmed that a dose of DM199 generated plasma concentrations of KLK1 similar to the standard IV dose of uKLK1.

ReMEDy1 was a randomized, double-blind, placebo-controlled, Phase 2 trial of 91 patients with acute ischemic stroke (AIS), demonstrated the safety and tolerability of DM199. In this Phase 2 trial, no statistically significant effects on overall efficacy outcomes were observed.

In this post hoc analysis, the effect of DM199 on the rate of stroke recurrence during a 90-day follow-up is assessed.

Methods

- Patients with mild-to-moderate AIS with onset ≤24 hours and National Institutes of Health Stroke Scale (NIHSS) score ≥6 and ≤25 were eligible.
- Patients were randomized to DM199 or placebo, given as a single 1 mcg/kg intravenous dose followed by 8 subcutaneous doses (3 mcg/kg) every 3 days for 22 days.
- For this post-hoc analysis, the primary outcome was occurrence of first subsequent ischemic stroke and/or stroke-related death during a 90-day follow-up.
- This report evaluated stroke recurrence from the ReMEDy1 trial (NCT03290560), which was conducted on 91 patients at 12 Hospital sites in Australia.
- Analysis of first recurrent ischemic stroke included all patients who underwent randomization and used a Cox proportional-hazards model with a factor for treatment group.

Results

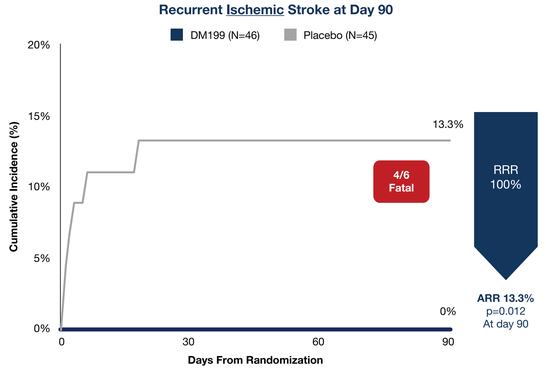
- Overall, 45 patients received placebo and 46 DM199 (Table 1).
- At baseline, patients were elderly with a median NIHSS score of 10.
- Mechanical thrombectomy (MT) was performed at first stroke in 28 patients (12 in the placebo group) and combined with tissue plasminogen activator (tPA) in 17 patients (5 in the placebo group) prior to enrollment. Patients with an NIHSS score ≥6 and ≤25 recorded at least one hour post initial therapy with MT / tPA were allowed to enrol in ReMEDy1.

Table 1. Baseline Characteristics

	Placebo (N=45)	DM199 (N=46)
Age, years (range)	71.7 (31-95)	69.9 (38-95)
Male Sex, n (%)	28 (62)	25 (54)
NIHSS Score, mean (median)	11.6 (9.0)	11.2 (10.0)
Treatment, n (%)		
tPA + Mechanical thrombectomy	12 (27)	5 (11)
Mechanical thrombectomy	12 (27)	16 (35)
tPA	8 (18)	13 (28)
Medical/Surgical History, n (%)		
Atrial Fibrillation	19 (42.2)	12 (25.5)
Hypercholesterolemia	14 (31.1)	14 (29.8)
Hypertension	32 (71.1)	32 (68.1)
Myocardial ischemia	10 (22.2)	7 (14.9)
Type 2 diabetes	11 (24.4)	11 (23.4)

- During the 90-days follow-up period, 6 out of 91(6.6%) participants experienced a recurrent ischemic stroke: 0 of 46 (0%) in the DM199 arm and 6 of 45 (13.3%) in the placebo arm (p=0.012; Hazard ratio: 8.002; 95% CI of ratio: 1.608 to 39.81) (Figure 2).
- DM199 resulted in absolute risk reduction (ARR) of 13.3% and relative risk reduction (RRR) of 100%.

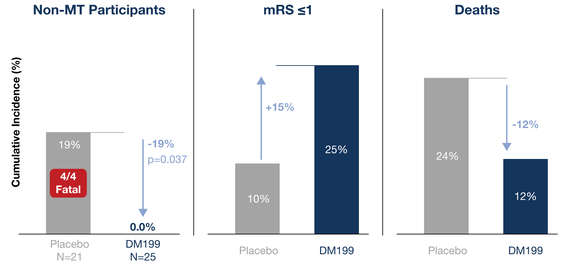
Figure 2. Cumulative Incidence of Recurrent Ischemic Stroke at Day 90



RRR = Relative risk reduction; ARR = Absolute risk reduction

- Treatment with DM199 within 24 hours of first AIS is associated with significant reduction in recurrent ischemic stroke by Day 90 (Figure 2). In those AIS patients who did not undergo MT, treatment with DM199 was associated with significant reduction in recurrent ischemic stroke as well as an increase in exceptional functional outcome at Day 90 (Figure 3).
- In patients not undergoing MT, DM199 reduced the absolute risk of stroke recurrence by 100% and the relative risk by 13.3% (Figure 3).
- 4 of the 6 recurrent strokes were fatal (all in the placebo group, p=0.056), all occurring in patients that did not undergo MT at the occasion of the primary stroke.
- The number needed to treat (NNT) was 7.5 to prevent one recurrent stroke in 90 days.
- Patients who had MT with occurrence of the primary stroke had a 2-fold reduction in stroke recurrence (8% vs. 19% in those who did not undergo MT), although this difference did not reach the statistical significance (p=0.32).
- One patient received DM199 following tPA experienced a severe hemorrhagic stroke.
- An additional sub-analysis was performed of the effect of DM199 independent of MT.
- In patients who did not undergo MT (21 and 25 in the placebo and DM199 arms, respectively)
  - 4 (19.0%) recurrent ischemic strokes occurred in the placebo arm (all fatal)
  - No recurrent ischemic strokes (0%) occurred in the DM199 arm (p=0.037)
  - Overall, the risk of death was reduced by 12% (absolute) with DM199.

Figure 3. AIS Patients Treated With DM199 and Who Did Not Undergo MT



Conclusions

- These ReMEDy1 Phase 2 study results are encouraging and suggest DM199 has the potential to reduce the risk of recurrent stroke at 90 days in AIS patients, regardless of initial treatment with or without tPA and/or MT.
- In addition, treatment with DM199 has the potential to improve stroke recovery and reduce stroke recurrence at 90 days in those AIS patients who are not clinical candidates for MT and warrants further investigation.
- A pivotal Phase 2/3 study with DM199, ReMEDy2, is ongoing in patients with AIS where tPA and or MT are not medically indicated to assess both stroke recovery and recurrence.

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