CTP16

Randomized, Double-blind, Placebo-controlled, Adaptive Design Study to Evaluate DM199 for the Treatment of Acute Ischemic Stroke (ReMEDy2 Trial)

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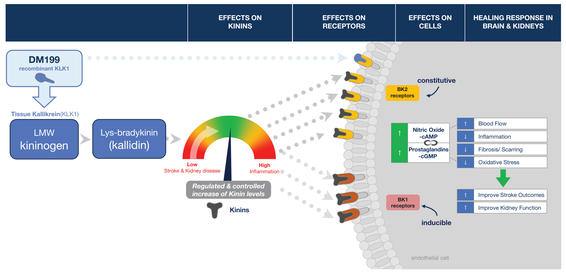
Introduction

Human tissue kallikrein-1 (KLK1) is a serine protease that plays a critical role in the regulation of systemic and regional blood flow via release of bradykinin from low molecular weight kininogen (Regoli and Gobeil, 2016; Naicker et al, 1999; Perez-Blanco et al, 1997). Moreover, KLK1 exerts pro-angiogenic and anti-inflammatory actions and mitigates oxidative stress (Alhenc-Gelas et al, 2019; Devetzi et al, 2018; Emanueli et al, 2001, 2004; Tschope et al, 2002; Mitchell et al, 2008). Urinary-derived KLK1 (uKLK1, trade name Kailikang®) was approved for the treatment of acute ischemic stroke (AIS) in China in 2005 (Nakayama et al, 1996). Meta-analyses demonstrate that initiating intravenous (IV) treatment with uKLK1 within 48hours of stroke onset improved neurological outcomes and survival in patients with AIS (Huang et al, 2020; Zhang et al, 2012).

DiaMedica Therapeutics has developed a recombinant version of human KLK1 (DM199) with the aim of delivering a therapeutic product endowed of higher efficacy and safety [note: uKLK1 associated with increased risk of hepatitis C, HIV and others] than uKLK1. The rationale behind the use of DM199 for treatment of AIS is that subcutaneous administration, instead of IV used with uKLK1 over 3 weeks, should restore low KLK1 levels to normal range to allow a regulated, sustained release of kinins and locally activated release of nitric oxide-cGMP and prostaglandin -cAMP improving stroke recovery from ischemia and reducing the risk of stroke recurrence (Figure 1). Data from a Phase 1 study 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.

Figure 1. Rationale for DM199 Replacement Therapy in AIS



The Phase 2 ReMEDy1 study recruited 91 patients with AIS, randomly assigned to DM199 (n=46) or placebo (n=45). Prior to enrollment, MT was performed in 21 patients of the DM199 group and 24 patients of the placebo group. Patients received a first dose of DM199 1 mcg/kg IV within 24 hours of AIS onset and then followed by 3 mcg/kg SC every 3rd day for 3 weeks. Outcomes were assessed at 90 days. None of the DM199-treated patients experienced a recurrent ischemic stroke during the follow-up, whereas AIS recurrence manifested in 6/45 (13%) of patients in the placebo group (p=0.013). Four of the six recurrent strokes, were fatal, and recorded in placebo treated patients who had not received MT (n=21) prior to enrollment in the study. Additionally, in the non-MT subgroup of DM199-treated patients, 36% (9/25) obtained an excellent functional outcome recovering to an NIHSS score of 0-1 compared with 14% (3/21) of patients in the placebo group (relative reduction 22%). Deaths in this same non-MT subgroup, including those caused by stroke recurrence, 24% in the placebo group 12% in the DM199 group, a 50% relative reduction.

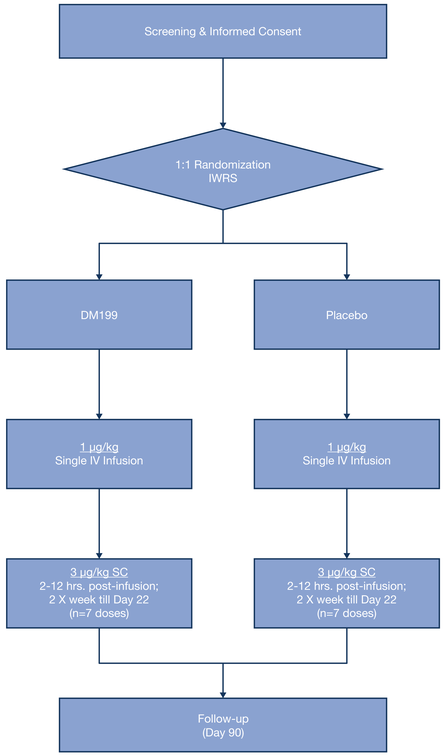
Objective

ReMEDy2 (NC0T5065216) is a pivotal clinical trial of DM199 in AIS patients evaluating both stroke recovery and the rate of stroke recurrence in patients for whom thrombolysis and/or a catheter-based procedure, mechanical thrombectomy (MT) is not medically appropriate.

Study Design

- Randomized, double-blind, placebo-controlled Phase 2/3 seamless adaptive design, multi-center study to evaluate the efficacy, safety and tolerability of DM199 (Figure 2).
- Randomized 1:1 to placebo or DM199 administered by a single intravenous (IV) dose followed by a subcutaneous (SC) dose within 12 hours and then 2 times a week till Day 22.
- The total duration of each participation in the study will be 90 days from the time of consent to completion of all study activities.

Figure 2. Study Design



Study Population

- AIS patients
  - Major selection criteria were based on learnings from the ReMEDy1 study (Table 1)

Table 1. Major Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Male or female ≥18 years of age	Received or scheduled to receive tPA
Diagnosed with AIS within 24 hours	Imaging findings consistent with LVO
Not a candidate for tPA	Received or scheduled to receive MT
Not a candidate for MT	Previous stroke
NIHSS ≥5 and ≤20	Currently prescribed ACEi and cannot be converted to another antihypertensive
Pre-morbid mRS score of 0-1 prior to stroke	

Study Endpoints

- Dual independent primary efficacy outcomes were selected to measure both AIS recovery and recurrent AIS.

Table 2. Outcome Measures For ReMEDy2

Primary Outcome Measures	Definitions
Efficacy (Two Independent Primary Endpoints)	
1. AIS Recovery	Excellent functional outcomes at Day 90 assessed as mRS score of 0 or 1
2. Recurrent AIS	Proportion of patients who experience a recurrent AIS by Day 90 assessed by a new, persistent neurological deficit attributable to cerebrovascular ischemia
Safety	Incidence of adverse events
Secondary Outcome Measures	
Mortality rate	Mortality over 90 days
Excellent neurological outcome	NIHSS score of 0 or 1 at Day 90
Excellent function independence	Barthel Index score ≥95 at Day 90
Disability	Distribution of mRS (shift) scores at Day 90
Tertiary Outcome Measures	
Excellent improvement	mRS at Day 21 (score of 0 or 1)
Disability	Distribution of mRS (shift) scores at Day 21
Excellent neurological outcome	NIHSS score of 0 or 1 at Day 21
Excellent function independence	Barthel Index score ≥95 at Day 21
Plasma and urine KLK1 levels	Baseline, Days 4, 21, 90
High-sensitivity C-reactive protein	Baseline, Days 4, 21, 90
Matrix metalloproteinase-9	Baseline, Days 4, 21, 90
Vascular endothelial growth factor	Baseline, Days 4, 21, 90
DM199 anti-drug antibodies	Baseline, Days 4, 21, 90

Study Analysis

- Planned enrollment of approximately 350 patients
- Sample size assumes:
  - 90% power at 14% absolute improvement in mRS excellent outcomes (0-1)
  - 90% power at 7% absolute reduction in stroke recurrence
- Interim analysis planned without interruption of enrollment

Interim Analysis

- An interim analysis will be conducted after approximately 144 patients complete their Day 90 assessments for Part A of the study.
- A Data Safety Monitoring Board (DSMB) will review the Part A interim data for efficacy and safety to determine if the trial will proceed into Phase 3.
- The adaptive feature of the study includes a formal interim assessment of efficacy and the possibility for increasing the sample size with guidance from DSMB.
- The study is initially planned to enroll an additional 220 patients in Part B (N=364 total). If sample size re-estimation is deemed appropriate from the interim analysis a maximum of 584 patients may be enrolled in Phase 3 (N=728 total).
- This adaptive design is (inferentially) seamless because it continues from Part A to Part B without pausing enrollment and because all (N=364 to 728 total) patients in the study will be included in the final statistical analysis.

Conclusions

- A significant unmet medical need exists for the treatment of AIS patients, both to improve functional recovery and reduce the rate of stroke recurrence.
- The need is most evident in those patients who are not eligible for thrombolysis and mechanical thrombectomy.
- This trial aims to confirm and expand the findings from the prior ReMEDy1 trial with stroke recovery and recurrence.
- Interim results from ReMEDy2 are expected in the first half of 2023 with final data in 2024 and should provide pivotal information on the efficacy of DM199 in patients with AIS.

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