DM199 (rinvecalinase alfa)

Investigational biologic for improving collateral circulation in ischemic stroke

DiaMedica Therapeutics is redefining the treatment paradigm for acute ischemic stroke (AIS) with their novel protein augmentation therapy, DM199.

As a recombinant form of the human tissue kallikrein-1 (KLK1) protein, DM199 works by augmenting KLK1 levels to improve collateral circulation in the penumbra and limit the damage caused by stroke.

The improvement of microcirculation in the penumbral region is predominantly facilitated through the enhanced activation of a crucial vasodilator receptor that focally upregulates in response to ischemia, leading to targeted improvement in regional blood flow and tissue preservation.

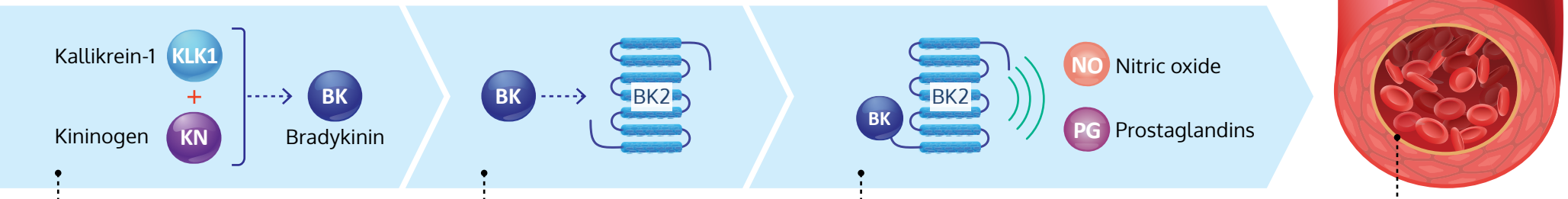
DM199 targets the vascular endothelium, obviating the need to cross the blood-brain barrier. Importantly, DM199/KLK1 has not been associated with an increased risk of severe intracranial hemorrhage.

In its phase 2 study, DM199 has demonstrated efficacy and safety in an expanded 24-hour treatment window, which is 5 times longer than the current 4.5 hours for tPA. DiaMedica initially aims to target patients ineligible for mechanical thrombectomy (MT) or tPA, potentially offering improved outcomes to a large number of patients who currently have no treatment option.

DiaMedica is currently enrolling in ReMEDy2, a Pivotal Phase 2/3 AIS clinical trial.

DiaMedica THERAPEUTICS

THE ROLE OF KLK1 IN VASCULAR HOMEOSTASIS



Tissue kallikrein-1 cleaves kininogen to release bradykinin peptide

BK binds to and activates the BK2 receptor

BK2 activation triggers the production of nitric oxide and prostaglandin

Blood vessel dilation

Ischemic stroke incidence and poor patient outcomes are independently associated with low levels of the KLK1 protein.[1, 2]

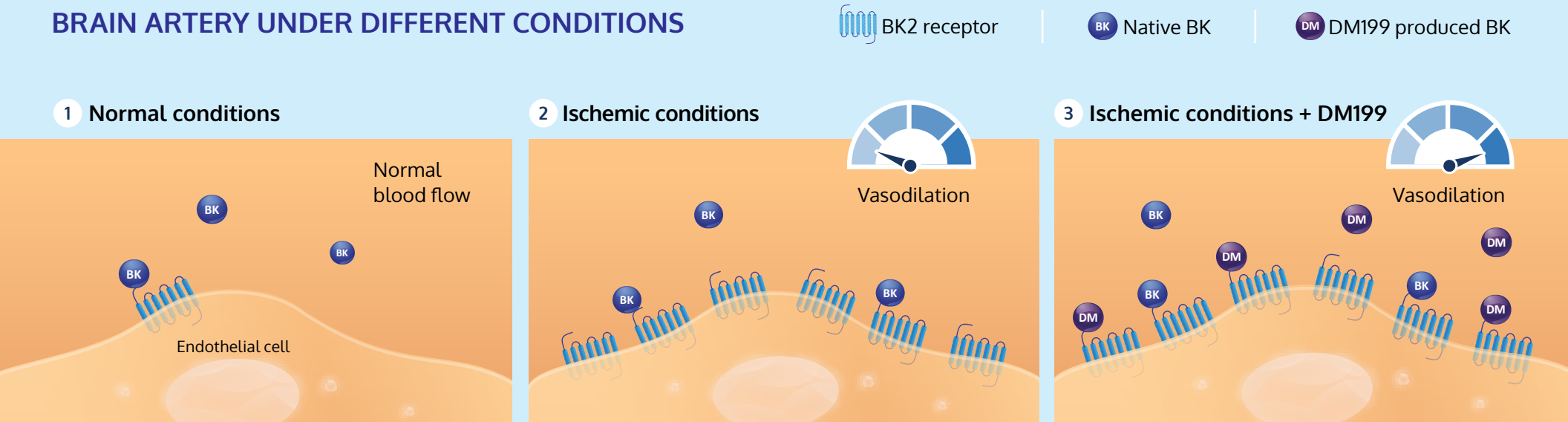
KLK1 is made predominantly in the kidneys and is the initiator of the critical vasodilation cascade. As KLK1 circulates in the blood, it cleaves low molecular weight kininogen to release the bradykinin (BK) peptide, a potent vasodilator. BK binds to its counterpart, the bradykinin 2 (BK2) receptor, to release nitric oxide (NO) & prostaglandins (PG) to dilate blood vessels and increase blood flow to the brain.

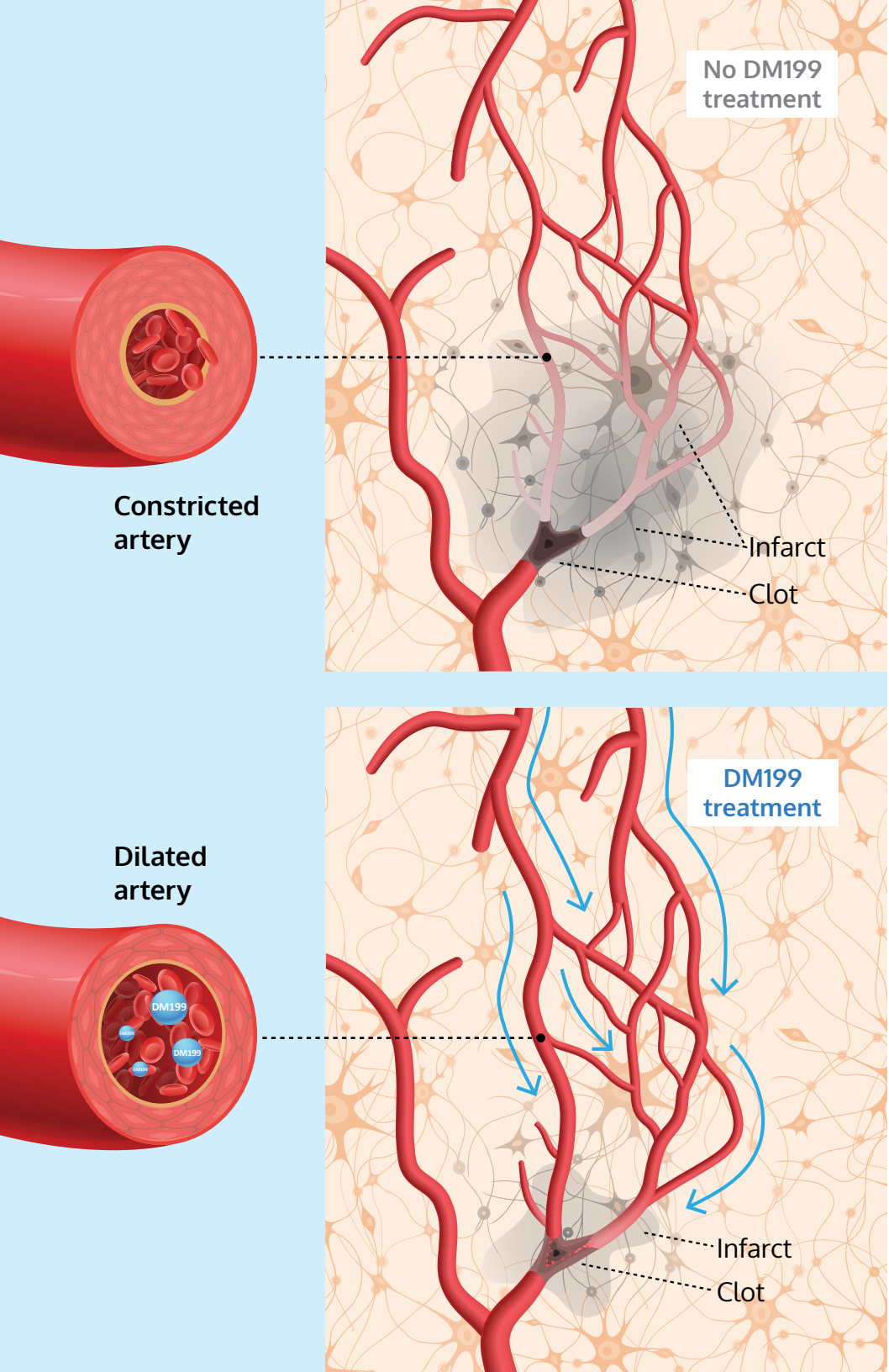
In response to an ischemic stroke, BK2 receptors are significantly upregulated (35-fold in animal models)[3] in the oxygen depleted brain arteries signaling the need for BK to bind and restore blood flow to the at-risk brain area.

DM199 enhances activation of the upregulated BK2 receptors to improve collateral circulation.

1. Annals of Neurology (2011) 70:265-73; https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.22404
2. Disease Markers (2019) Volume 2019, Article 5289715; https://doi.org/10.1155/2019/5289715
3. PLOS ONE (2018), 13(6), e0198553. https://doi.org/10.1371/journal.pone.0198553

BRAIN ARTERY UNDER DIFFERENT CONDITIONS





HOW DM199 IMPROVES COLLATERAL CIRCULATION

The novel DM199 mechanism of action mimics the behavior of endogenous KLK1 to facilitate the release of endothelial nitric oxide and prostaglandins to preferentially vasodilate arteries in the ischemic penumbra, increase collateral blood flow, and improve overall function of critical processes.

Administered intravenously or subcutaneously, DM199 travels in the blood and targets the BK2R expressed on endothelial cells, eliminating the requirement to cross the blood-brain barrier like most neuroprotectants. DM199 acts rapidly to increase collateral circulation in the ischemic penumbra, and its biologic mechanism of action lowers the risk for off-target effects common with small molecules. DM199 can potentially preserve tissue and neuronal function, reduce infarct size, prevent or minimize permanent brain damage, and reduce risk of stroke recurrence over 90 days, which is often highly disabling.

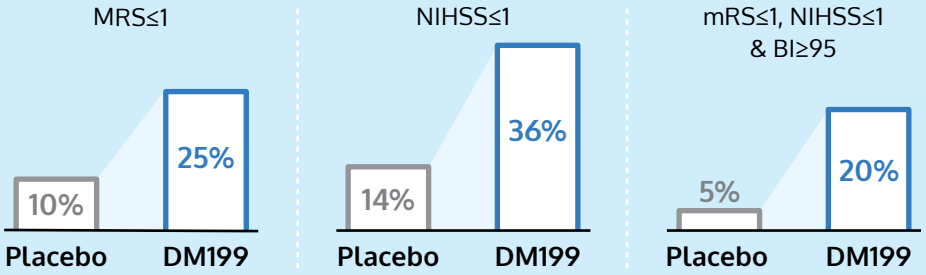
Over the past decade in China, substantial proof of principle has been established for augmenting KLK1 levels to enhance collateral circulation and improve outcomes in AIS. Since a large amount of KLK1 is synthesized in the distal nephron of the kidney, a small portion of this glycoprotein is excreted in the urine. Safe and effective, human urinary KLK1 is approved in China for AIS and has been extensively used to treat over 600K AIS patients* annually. Over 200 clinical studies in China have found it effective for increasing blood flow, decreasing ischemia in the penumbra, and reducing infarct size. Importantly, human urinary KLK1 has not been shown to increase the risk of severe intracranial hemorrhage.

*under Shanghai Pharmaceuticals Kailikang®

DM199 ReMEDy1 AIS PHASE 2 STUDY*

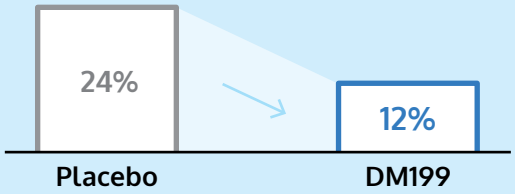
Placebo N=21 DM199 N=25

Excellent outcomes (mRS≤1, NIHSS≤1 & Global) (% of patients at day 90*)



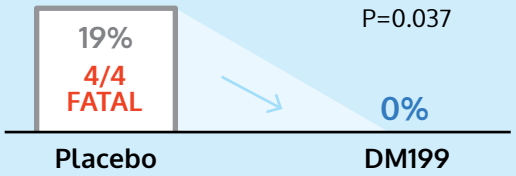
Absolute improvement
15% mRS, 22% NIHSS and 15% (mRS, NIHSS, BI)

Deaths (% of patients at day 90*)



Absolute decrease –12%

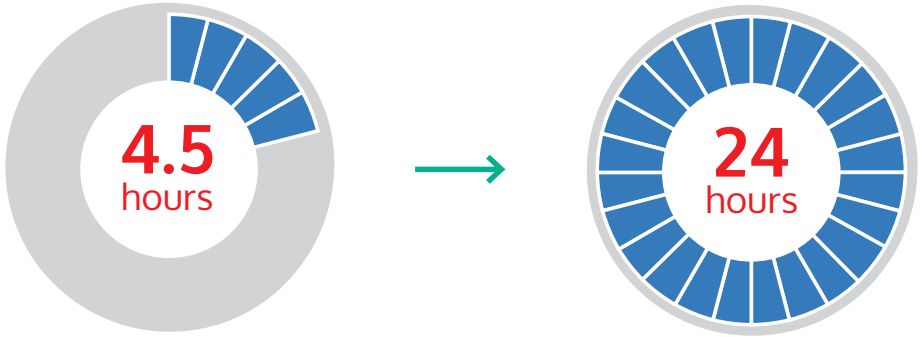
Stroke-in evolution / recurrent ischemic events (% of patients at day 90)



Absolute decrease –19%

*not pretreated with mechanical thrombectomy (MT)

5X TREATMENT WINDOW EXPANSION VS TPA



tPA DM199

In our Phase 2 study, DM199 demonstrated a positive safety profile, and, in participants not receiving mechanical thrombectomy prior to enrollment, significantly increased efficacy while expanding the treatment window to 24 hours. Additionally, treatment with DM199 showed a clinically significant reduction in stroke recurrence and death rates. Patients were dosed on average at 18 hours after AIS.

ReMEDy2 PHASE 2/3 AIS STUDY

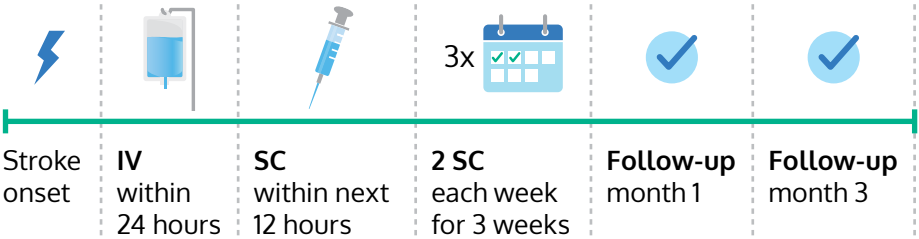
The ReMEDY2 Phase 2/3 study is investigating DM199 for improving functional recoveries in AIS patients within an expanded 24-hour treatment window.

364 participants

Up to 100 locations globally

1:1 randomized (placebo vs DM199)

Trial design:



Stroke onset	**IV** within 24 hours	**SC** within next 12 hours	**2 SC** each week for 3 weeks	**Follow-up** month 1	**Follow-up** month 3

Primary endpoint: Modified Rankin Score (mRS) 0-1

Contact information:

If you have any questions or would like to learn more about DM199 and the ReMEDy2 study, please contact:

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DiaMedica THERAPEUTICS

The safety and effectiveness of DM199 for the treatment of acute ischemic stroke has not been established and is limited to investigational use only.