

ReMEDy2 Updates

November 13, 2023



Summary of ReMEDy2 Trial Protocol Key Changes

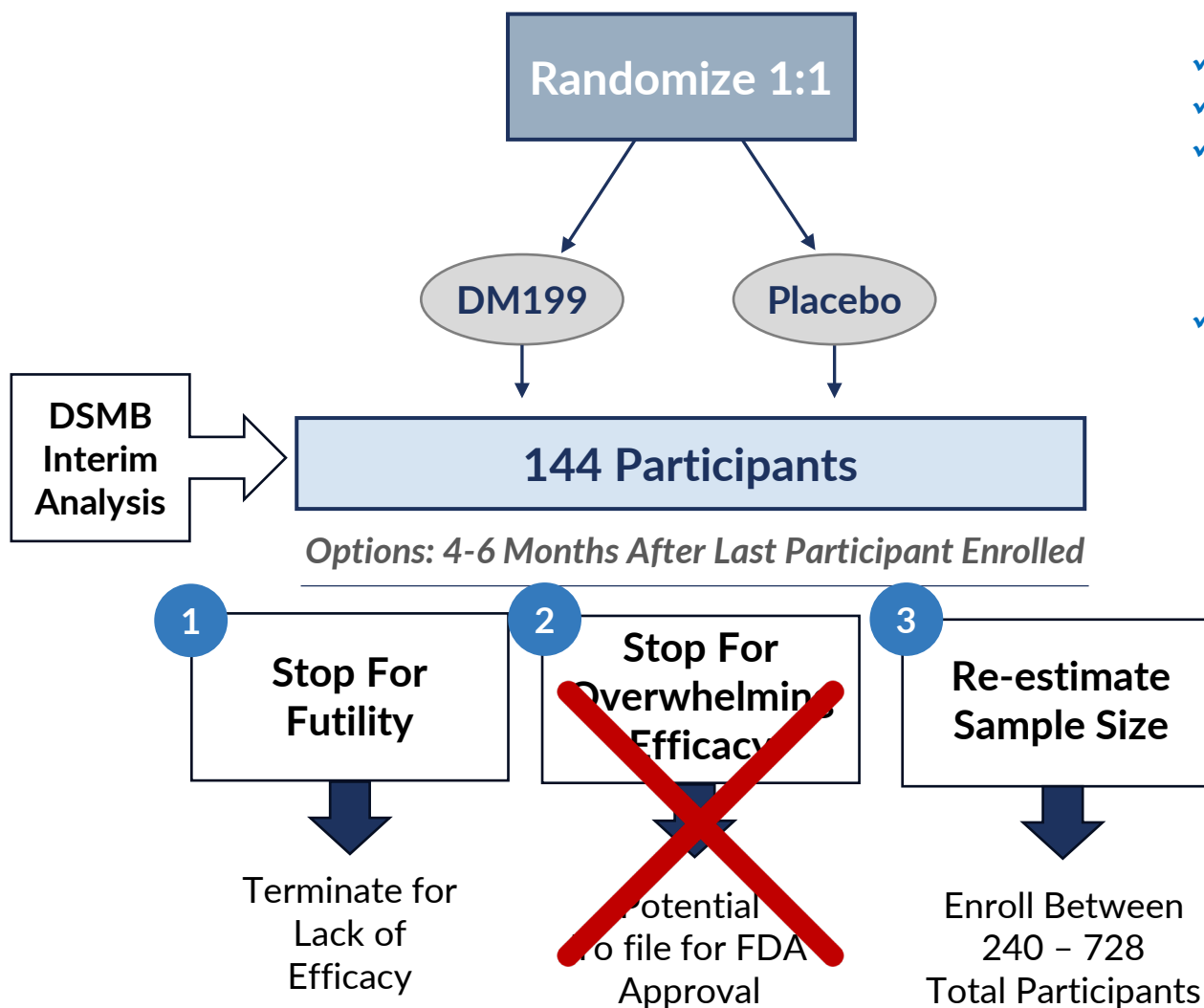
Inclusion Criteria Guided by Recent Insights from KOLs & the Marketer of Urinary KLK1 in China

- **Changes to inclusion criteria aimed at enhancing the probability of clinical success:**
 - Modified NIHSS baseline inclusion criteria to 5-15 (6-25 in ReMEDy1; see slides 4 & 5 for rationale)
 - Estimate a net reduction of approximately 45,000 potential participants in the US (~6% of all AIS patients)
 - Excluded posterior circulation strokes (see slide 6 for rationale)
 - *Modifications not expected to meaningfully prolong enrollment timetable*
- **Eliminate the option to stop for overwhelming efficacy at the interim analysis**
 - Reduces statistical alpha penalty which enhances probability of success
 - Provides larger safety data set and increases probability of achieving statistical significance on secondary endpoints
 - By the time the interim analysis is available, enrollment should already be near 240 participants – minimal benefit to overall timeline
 - 240 participants is the bottom end of the sample size readjustment range of 240 – 728 participants (see slide 3)
- **DiaMedica is confident that targeting moderate strokes is the fastest path to approval with the greatest likelihood of success. Post-approval further label expansion studies:**
 - Mild and severe strokes (different study endpoints)
 - Adjuvant therapy with thrombolytics

Change to ReMEDy2 Clinical Trial Interim Analysis Plan

Eliminating option 2, stopping for overwhelming efficacy at the interim analysis (IA), but adaptive design framework remains in place

Adaptive design allows for an adjustment in the sample size based on treatment effect



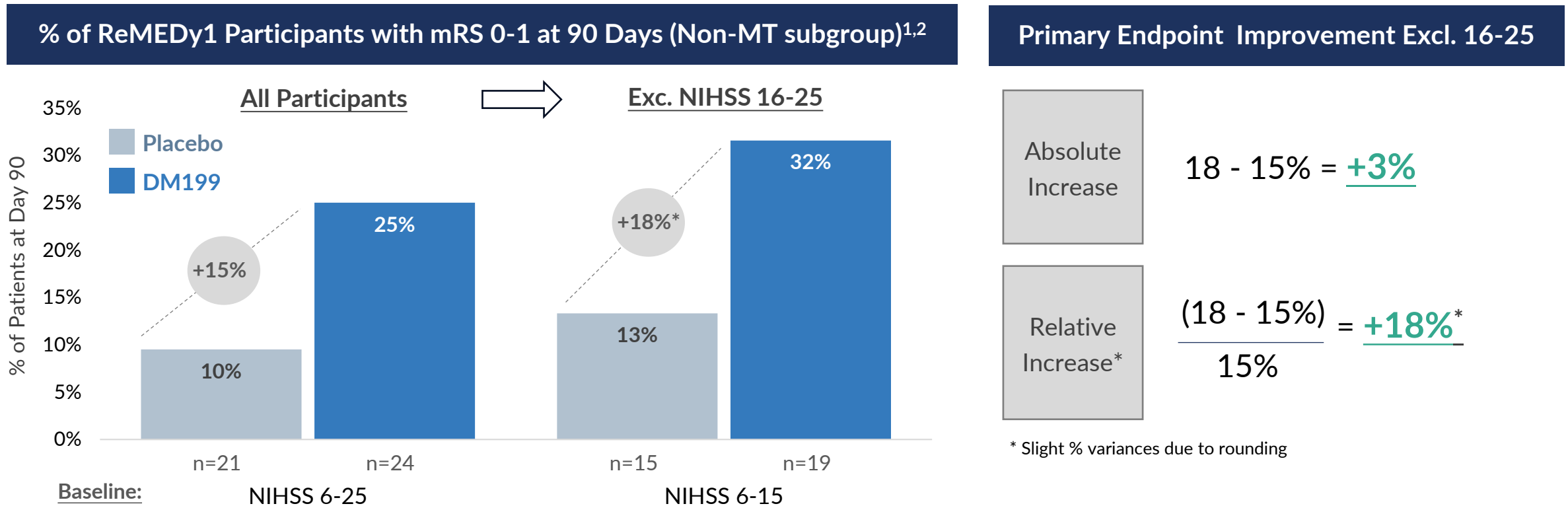
Rationale

- ✓ Reduce statistical alpha penalty
- ✓ Larger safety database
- ✓ Increases PoS* of winning on secondary endpoints which would provide more robust efficacy for the BLA package
- ✓ Enrollment should already be near 240 participants at completion of IA, the bottom end of re-estimate range

Potential Benefit Of Excluding Baseline NIHSS 16-25 Participants

~3% Absolute/18% Relative Increase in mRS 0-1 in ReMEDy1 Phase 2 Post Hoc Analysis

- Percentage of DM199 participants achieving mRS 0-1 relative to placebo increased when more severe strokes (NIHSS 16-25) were excluded
- Achieving mRS 0-1 from above baseline NIHSS 15 is a high bar, and no participants in ReMEDy1 Phase 2 (Non-MT) achieved mRS 0-1
- Potential to enhance primary endpoint measure and interim analysis powering by excluding NIHSS 16-25 from ReMEDy2 Phase 2/3

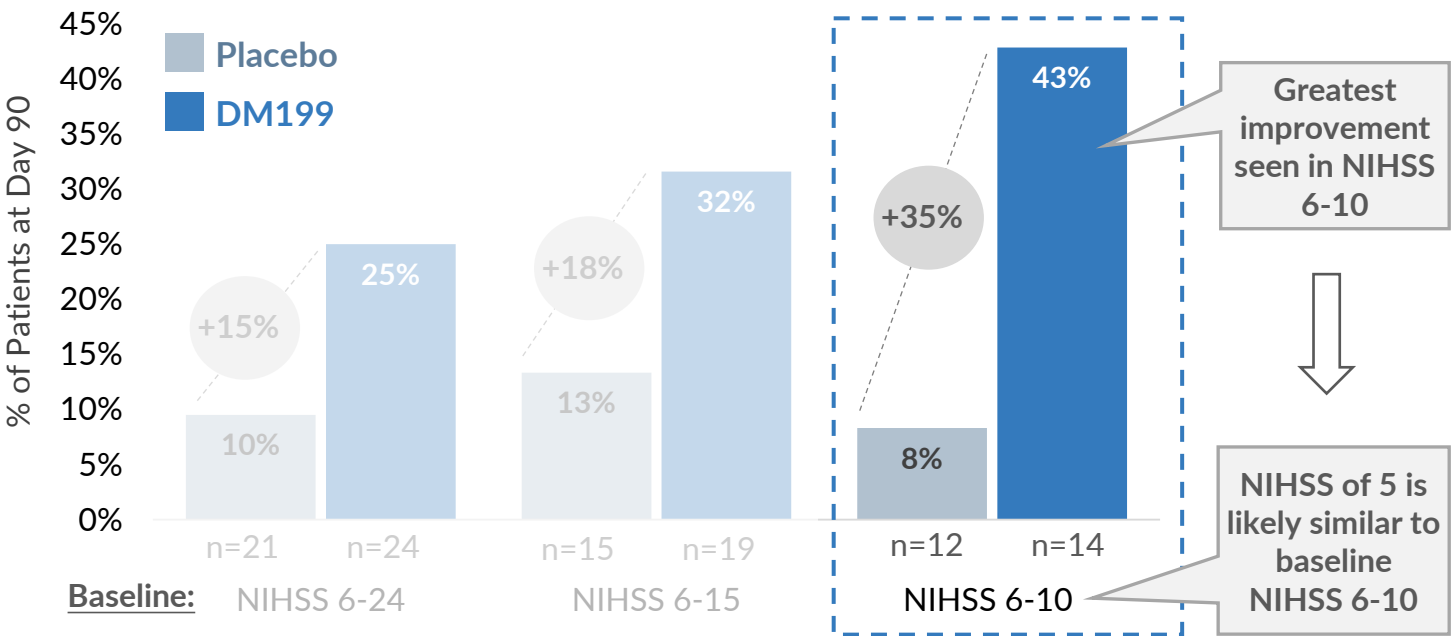


Potential Benefit of Adding NIHSS 5 to the ReMEDy2 Study

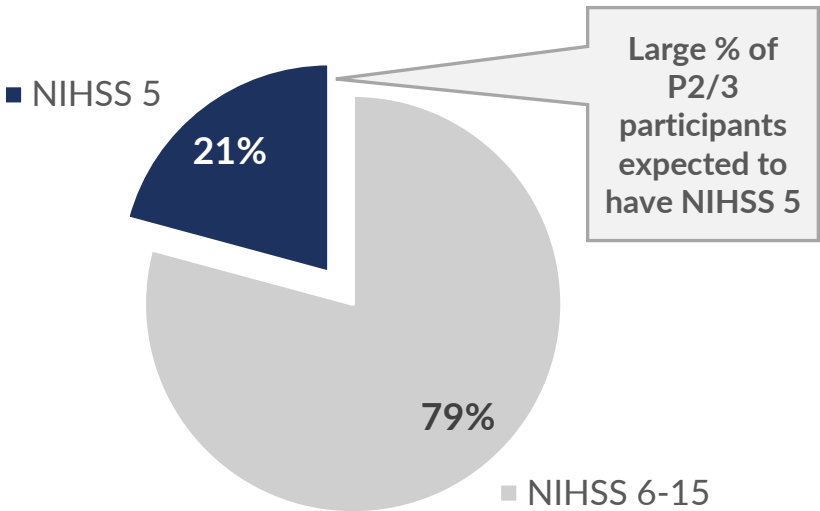
Large Pool of Eligible Patients with NIHSS 5 with Potential to Improve Performance vs. Placebo

- Greatest improvement in the primary endpoint was observed in participants with baseline NIHSS 6-10 in the ReMEDy1 Phase 2 (non-MT)
- By incorporating participants with baseline NIHSS 5 into ReMEDy2, we believe we will capture more of these high responding participants
- Stroke patients with NIHSS of 5 represent approximately 20% of all moderate strokes
- Including mild strokes (NIHSS < 5) may erode treatment effect due to high placebo response

% of ReMEDy1 Participants with mRS 0-1 at 90 Days
(Non-MT, Post Hoc Analysis of NIHSS 6-10 Baseline) ^{1,2}



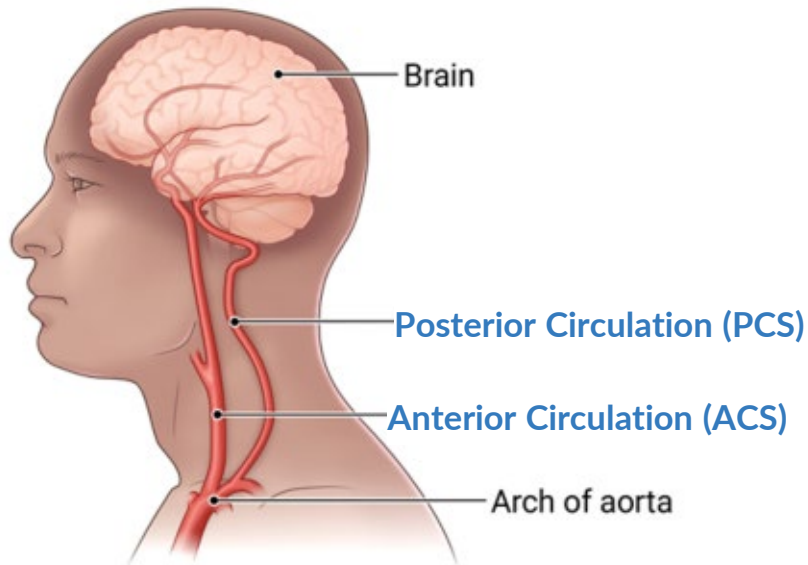
Distribution of Moderate Strokes¹



Potential Benefit of Excluding Posterior Circulation Strokes (PCS)

Consistent with Urinary KLK1 Inclusion/Exclusion Criteria of KLK1 Studies in China

- It has been observed that approximately 80% of ischemic strokes are attributed to the anterior circulation (ACS), while around 20% are associated with the posterior circulation¹
- Additionally, it is estimated that approximately 70%² of PCS present in patients with a baseline NIHSS ≤ 4
 - Since ReMEDy2 enrollment criteria is 5-15, the overall reduction to the eligible patient pool is minimized
- Recent feedback from Chinese KOLs familiar with urinary KLK1 (uKLK1) supports excluding PCS, and this was corroborated by US KOLs
- **Importantly**, PCS were excluded in the original uKLK1 Chinese approval study and the recent 2021 RESK study (1,200 participants on uKLK1)⁴



Additional Rationale For Excluding PCS

1. NIHSS is strongly weighted towards deficits caused by anterior circulation strokes (ACS), hence PCS severity may be understated by NIHSS¹
2. Eliminate the potential for randomization imbalances, ensuring a more homogenous study population and consistent therapeutic outcome
3. PCS was associated with worse outcomes compared with ACS in patients arriving later than 4.5 hours at hospital – Vast majority of DM199 patients expected to be dosed after 4.5 hours³

1. Alemseged et al (2022), Posterior NIHSS Improves Prognostic Accuracy in Posterior Circulation Stroke. Stroke. 2022;53:1247–1255. DOI:10.1161/STROKEAHA.120.034019
2. Siniscalchi, et al (2017). The National Institutes of Health Stroke Scale: Its Role in Patients with Posterior Circulation Stroke, Hospital Topics, 95:4, 79-81, DOI: 10.1080/00185868.2017.1322888
3. Sommer et al (2018). Is Functional Outcome Different in Posterior and Anterior Circulation Stroke? Stroke 2018. DOI: 10.1161/STROKEAHA.118.021785
4. CNS Neurosci Ther. 2021;27:1493–1503