

APPLICATION OF THE HERMES-24 SCORE FOR IMPROVING ACUTE ISCHEMIC STROKE DRUG TRIALS: EVALUATING PP-007 AND THE HEMERA STUDY

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PROLONG

ABSTRACT

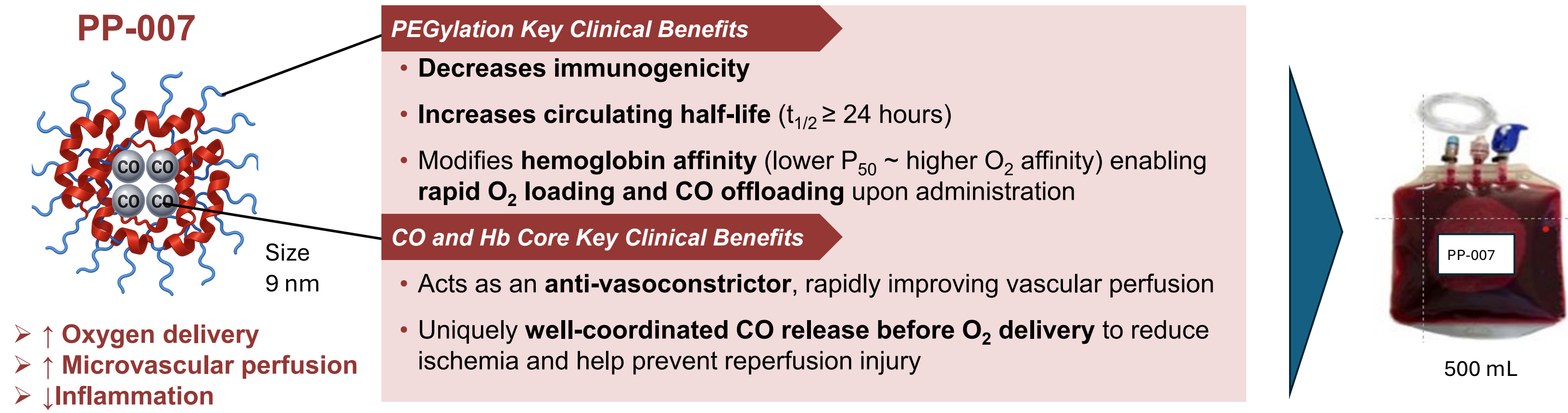
Background: The ongoing PP-007 HEMERA-1 study (NCT04677777) has shown good safety and efficacy signals for AIS with standard of care (MT ± IVT), and a Phase 3 adaptive design trial is in development. The HERMES-24 score (Tanaka et al. Stroke, 2025) is a clinical tool that predicts 90 d mRS outcomes after A-LVO stroke based on early (24 h) data. HERMES-24 = age (yr)/10 + NIHSS 24h was found to be highly predictive for 90 d mRS on validation and may provide clinicians with a prognostic aid in treatment discussions. We sought to evaluate the potential of HERMES-24 scoring as a predictive aid in AIS drug trials.

Methods: The HEMERA-1 data was used to determine if this treatment-agnostic predictive score may expedite interim analysis and de-risk trial conduct. The HERMES-24 scores were determined for HEMERA-1 (n=47) that yielded subject-specific 90 d mRS predictions and compared to actual, observed mRS values to assess the utility of the HERMES-24 prediction paradigm and the relative trajectory of outcomes of HEMERA-1 subjects from 24 h to 90 d.

Results: Predictive capability of the HERMES-24 score for HEMERA-1 was high, with a c-statistic of 0.937 (95% CI 0.848-1.000) for prediction of mRS 0-2 in HEMERA-1 that compared favorably to the c-statistic of 0.914 (95% CI, 0.886–0.944) observed for the original HERMES-24 validation. Both data sets mRS 0-2 descended markedly with increasing HERMES-24 scores but HEMERA-1 subjects tended to outperform HERMES-24 predictions. HEMERA-1 subjects between 15 and 20 on the HERMES-24 score scale (Figure 1) had better mRS outcomes than expected. Overall, 70% (33/47) of HEMERA-1 subjects achieved mRS 0-2 at 90 d v. 57% predicted by their HERMES-24 scores.

Summary: These findings suggest that subjects treated with PP-007 may have more favorable trajectories of recovery from 24 h to 90 d than otherwise expected and support the use of HERMES-24 scoring as an early interim analysis tool. To our knowledge, this represents the first application of the HERMES-24 score with an investigational drug product. The PP-007 Phase 3 adaptive enrichment trial includes a pre-defined interim analysis of 90 d mRS, and the ability to use 24 h scores of high predictive power may facilitate earlier, robust decision-making shortening trial times while increasing chances for a successful trial outcome. Finally, the treatment-independence and simplicity of the scoring system may extend the use of HERMES-24 to other AIS treatments in development, including resource-constrained settings.

PP-007 OVERVIEW



PP-007, PEGylated carboxyhemoglobin (aka SANGUINATE®) is an investigational drug product and not approved for treatment of any condition

BASELINE CHARACTERISTICS

Baseline Characteristic	PP-007+SoC (N=47)	A-LVO (N=40)	Non-A-LVO (N=7)
Age (years)			
n	47	40	7
Mean (SD)	71.8 (14.33)	72.9 (15.03)	65.6 (7.37)
Median	75	76	66
Min, Max	29, 95	29, 95	53, 76
Gender, n (%)			
Male	25 (53.2)	21 (52.5)	4 (57.1)
Female	22 (46.8)	19 (47.5)	3 (42.9)
NIHSS			
n	47	40	7
Mean (SD)	14.9 (5.23)	16.1 (4.75)	8.4 (2.23)
Median	15	16	7
Min, Max	6, 26	6, 26	6, 12
ASPECTS			
n	45	40	5
Mean (SD)	7.1 (1.60)	7.0 (1.65)	8.0 (0.71)
Median	7	7	8
Min, Max	2, 10	2, 10	7, 9
Stroke Type/Location			
Anterior circulation LVO	40 (85.1)	40 (100.0)	0
Intracranial ICA	2 (4.3)	2 (5.0)	0
M1-M2 MCA	2 (4.3)	2 (5.0)	0
M1-MCA	22 (46.8)	22 (55.0)	0
M1-MCA and intracranial ICA	2 (4.3)	2 (5.0)	0
M2-MCA	12 (25.5)	12 (30.0)	0
Posterior circulation LVO	2 (4.3)	0	2 (28.6)
No LVO	5 (10.6)	0	5 (71.4)
M2-MCA	1 (2.1)	0	1 (14.3)
Duration from TLKW to IVT start (hours)			
n	24	19	5
Mean (SD)	2.048 (0.9837)	1.784 (0.7667)	3.054 (1.1499)
Median	1.7	1.5	3.5
Min, Max	0.90, 4.05	0.90, 3.27	1.17, 4.05
Duration from TLKW to MT start (hours)			
n	38	36	2
Mean (SD)	7.997 (5.6466)	7.871 (5.6820)	10.280 (6.2225)
Median	5.875	5.82	10.28
Min, Max	1.58, 21.92	1.58, 21.92	5.88, 14.68
Duration from TLKW to PP-007 start (hours)			
n	46	39	7
Mean (SD)	10.780 (6.7250)	10.688 (6.3850)	11.294 (8.9798)
Median	8.84	9.1	7.43
Min, Max	1.62, 30.00	1.62, 24.45	4.98, 30.00

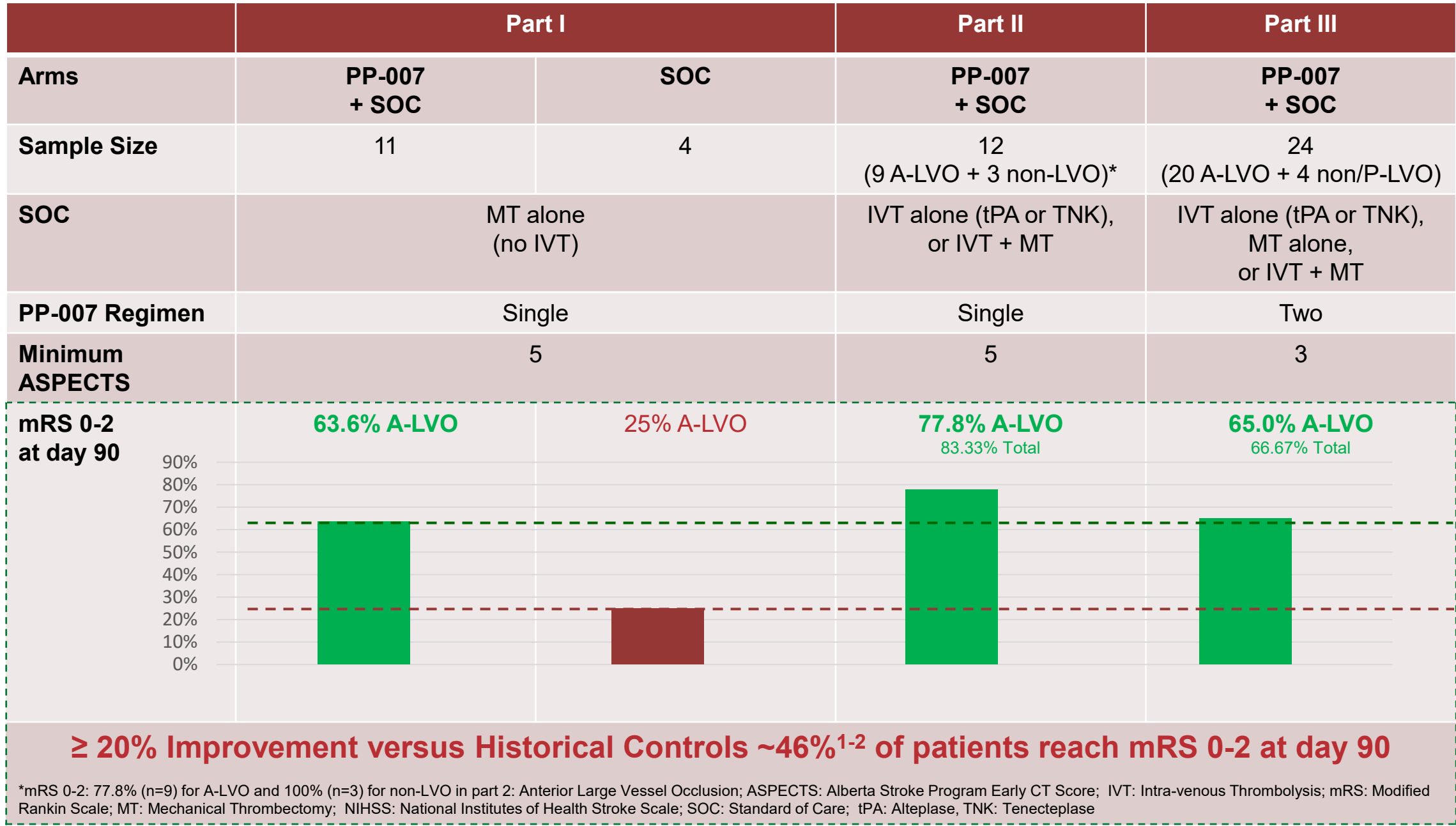
HEMERA-1 TRIAL DESIGN

Study Design	- Multi-part, prospective, randomized, open-label Phase 1/2 study evaluating PP-007 as an adjunct to standard of care (SOC: intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT)) - Enrollment from 2021 - 2024 with last-patient-last-visit in 2025			
Indication	Acute ischemic stroke (AIS) due to anterior circulation large vessel occlusion (A-LVO)			
Sample Size	N = 51 total N = 47 treated with PP-007 vs. N = 4 SOC			
Treatment Arms	Part 1*	Part 2	Part 3	
	Arm 1: PP-007 + SoC N=11 A-LVO	Arm 2: Placebo + SoC N=4	Arm 1: PP-007 + SoC N=12 (9 A-LVO + 3 non-LVO)	Arm 1: PP-007 + SoC N=24 (20 A-LVO + 4 non/P-LVO)
SOC Arms	MT (No IVT)		IVT alone <i>or</i> IVT + MT	IVT alone <i>or</i> MT alone <i>or</i> IVT + MT
PP-007 Doses	Single		Single	Two (24 ± 6 hours after 1 st dose*)
Administration	320 mg/kg IV infusion (max 500mL) over 2 hours			
Primary Endpoints	Safety (in addition to ~300 human subjects dosed across prior studies)			
Secondary Endpoints	- Good functional outcome at Day 90, defined as a mRS score of 0-2 - Early Response, defined as a 10-point decrease or score of 0-1 on NIHSS through Day 5-7/hospital discharge - ASPECTS			
Geography	USA			

SAFETY OUTCOMES

HEMERA-1 Safety Results	Part I						Part II			Part III		
Doses	Single-dose						Single-dose			Two-dose		
Standard of Care	Mechanical thrombectomy (No IVT)						IVT alone (tPA or TNK), or IVT + MT			IVT alone (tPA or TNK), MT alone, or IVT + MT		
Arms	Arm 1 (n=11) PP-007 + SoC			Arm 2 (n=4) SoC			Arm 1 (n=12) PP-007 + SoC			Arm 1 (n=24) PP-007 + SoC		
	n	%	E	n	%	E	n	%	E	n	%	E
Total TEAEs	10	90.9	39	4	100.0	12	9	75.0	31	24	100	234
Related TEAEs	3	27.3	3	0	0	0	7	58.3	7	16	66.7	34
Serious TEAEs	4	36.4	8	2	50.0	2	4	33.3	4	10	41.7	10
Fatal TEAEs	1	9.1	1	1	25.0	1	0	0	0	3	12.5	3

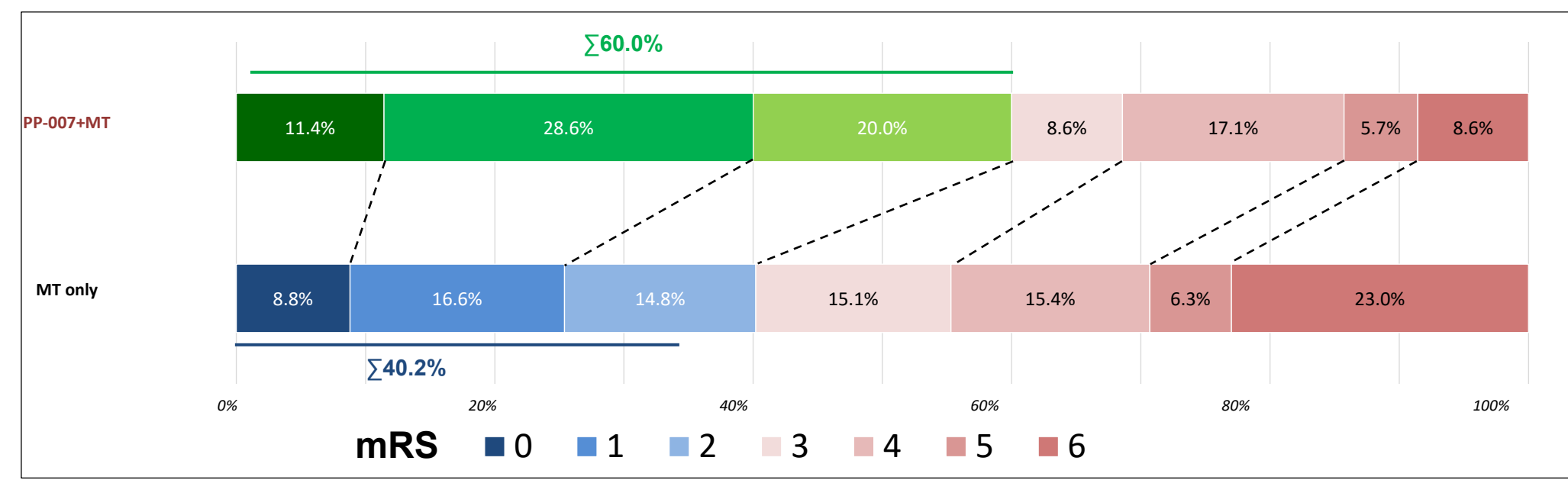
EFFICACY OUTCOMES mRS



HEMERA-1 MATCHED ANALYSIS

HERMES / AURORA (N=1,067 vs. 35)

- 90-day mRS 0-2: 60.0%* PP-007+MT vs. 40.2%
- Odds Ratio: ~2.27 (post-stratification) vs. 1.66 (pre-stratification)



EFFICACY OUTCOMES NIHSS

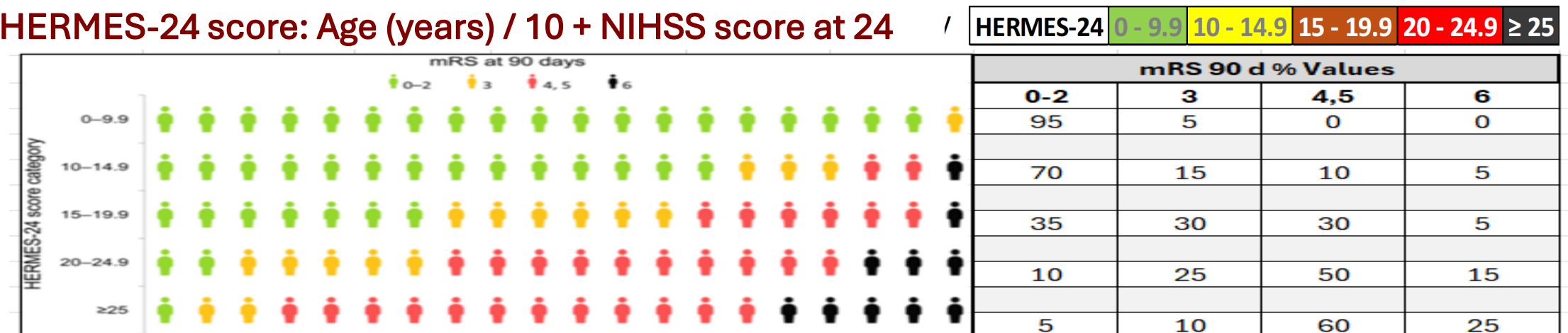
HEMERA-1 Results	Part I		Part II		Part III	
Arms	Arm 1 PP-007+SOC	Arm 2 SOC	Arm 1 PP-007+SOC	Arm 1 PP-007+SOC	Arm 1 PP-007+SOC	Arm 1 PP-007+SOC
	N=11	N=4	Total N=12*	A-LVO N=9	Total N=24*	A-LVO N=20
PP-007 Dose	Single		Single		Two	
mRS 0-2 at day 90	63.6% (7)	25% (1)	83.3% (10)	77.8% (7)	66.7% (16)	65.0% (13)
NIHSS Early Response at Day 5/7 or Hospital Discharge (N)	63.6% (7)	25.0% (1)	50.0% (6)	55.6% (5)	45.8% (11)	50.0% (10)
Mean change (SD) from baseline to:						
Day 90 NIHSS	-14.50 (10.368)	-7.00 (11.000)	-10.80 (4.158)	-11.63 (4.069)	-10.44 (4.871)	-11.40 (4.840)
Higher decline (better)						
24-hour ASPECTS	-0.18 (1.250)	-1.5 (3.000)	NA	NA	NA	NA
Less decline (better)						

HERMES-24 SCORING

CLINICAL AND POPULATION SCIENCES

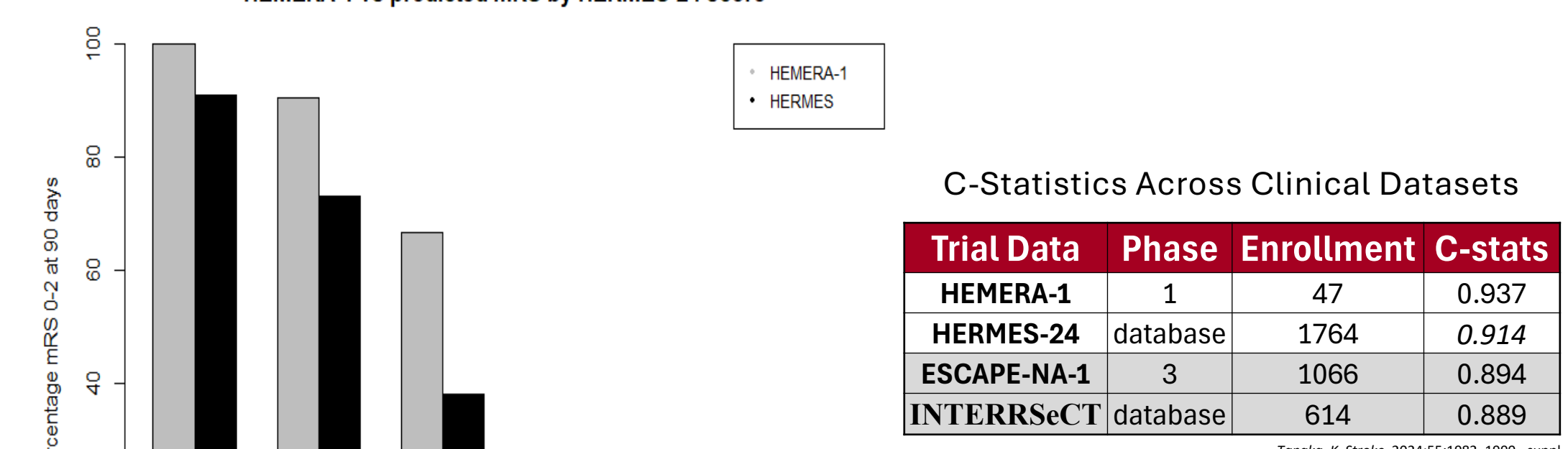
HERMES-24 Score Derivation and Validation for Simple and Robust Outcome Prediction After Large Vessel Occlusion Treatment

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Part	Subject ID	Treatment Grp	Age	NIHSS 24 hr	mRS 90d	HERMES-24 Score	Color Code
I	001-001	SOC	73	21	4	28.3	
	001-002	PP-007 + SOC	91	2	1	11.1	
	001-004	PP-007 + SOC	84	6	3	14.4	
	001-005	PP-007 + SOC	71	4	1	11.1	
	001-006	PP-007 + SOC	83	5	0	13.3	
	002-001	PP-007 + SOC	60	9	2	15.0	
	003-001	PP-007 + SOC	84	15	4	23.4	
	003-002	SOC	74	10	0	17.4	
	003-003	SOC	90	14	6	23.0	
	003-004	PP-007 + SOC	45	19	4	23.5	
II	003-005	SOC	71	20	3	27.1	
	003-006	PP-007 + SOC	70	6	1	13.0	
	004-001	PP-007 + SOC	76	6	2	13.6	
	004-002	PP-007 + SOC	76	4	1	11.6	
	006-001	PP-007 + SOC	58	20	5	25.8	
	001-201	PP-007 + SOC	95	10	4	19.5	
	001-202	PP-007 + SOC	94	2	2	11.4	
	003-202	PP-007 + SOC	71	23	4	30.1	
	003-203	PP-007 + SOC	80	14	2	22.0	
	003-204	PP-007 + SOC	29	15	2	17.9	
III	003-205	PP-007 + SOC	80	3	2	11.0	
	003-206	PP-007 + SOC	68	6	1	12.8	
	003-207	PP-007 + SOC	66	0	1	6.6	
	003-208	PP-007 + SOC	29	1	1	3.9	
	003-209	PP-007 + SOC	53	5	2	10.3	
	003-210	PP-007 + SOC	76	4	0	11.6	
	003-211	PP-007 + SOC	75	2	1	9.5	
	001-301	PP-007 + SOC	78	3	1	10.8	
	001-302	PP-007 + SOC	78	5	1	12.8	
	001-303	PP-007 + SOC	60	3	1	9.0	
IV	001-304	PP-007 + SOC	68	1	0	7.8	
	001-305	PP-007 + SOC	89	5	0	13.9	
	003-301	PP-007 + SOC	80	22	6	30.0	
	003-302	PP-007 + SOC	62	5	2	11.2	
	003-303	PP-007 + SOC	67	9	1	15.7	
	003-304	PP-007 + SOC	78	7	2	14.8	
	003-305	PP-007 + SOC	64	6	1	12.4	
	003-306	PP-007 + SOC	84	7	0	15.4	
	003-307	PP-007 + SOC	69	18	5	24.9	
	003-308	PP-007 + SOC	95	8	4	17.5	
V	003-309	PP-007 + SOC	89	17	4	25.9	
	003-310	PP-007 + SOC	61	5	3	11.1	
	003-311	PP-007 + SOC	64	16	3	22.4	
	003-312	PP-007 + SOC	82	17	3	25.2	
	003-313	PP-007 + SOC	75	0	0	7.5	
	004-301	PP-007 + SOC	63	17	4	23.3	
	004-302	PP-007 + SOC	71	1	0	8.1	
	004-303	PP-007 + SOC	76	0	0	7.6	
	004-304	PP-007 + SOC	77	5	2	12.7	
	009-301	PP-007 + SOC	66	5	1	11.6	
009-302	PP-007 + SOC	64	3	2	9.4		

KEY: Blue Type: SoC Grp Red Type: Last observation carried forward



HEMERA-1 STUDY SUMMARY

PP-007 HEMERA-1 enrolled broad study demographics and SoC treatment population

- Overall showed good safety and tolerability

Efficacy Measures – Modified Rankin and National Institutes of Health Stroke Scores

mRS exhibited strong improvements $\geq 20\%$ mRS 0-2 at 90 days

- Observed in 1. Part 1 RCT 2. Historical controls & 3. Matched analysis (HERMES & AURORA)

NIHSS Early response (>10 -point drop) trended similar to mRS

Could HERMES-24 Score be used to evaluate early responses in a clinical trial?

- HERMES-24 Scoring showed similar trend to improvements v. SoC with good C-statistics

Further Investigation of HERMES-24 in RCT is warranted

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