ARPEGGIO Trial of Scp776 Adjunctive to Thrombectomy:
Efficacy Patterns in a Late Window Phase 2a Population

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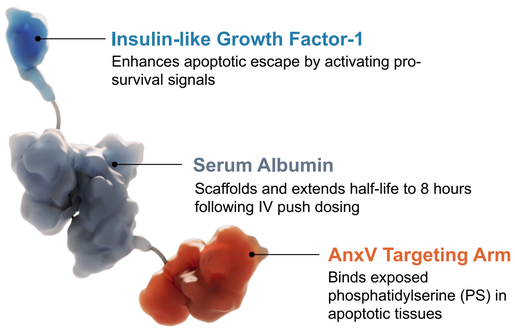
ARPEGGIO Study of Scp776 in AIS Indicated for EVT



Scp776 is a *first-in-class* cerebroprotective biologic that binds phosphatidylserine (PS) on apoptotic cells to deliver IGF-1 as an adjunct to endovascular thrombectomy (EVT).

ARPEGGIO is a *signal-seeking* phase 2a study in EVT-eligible large-vessel-occlusion (LVO) patients excluded from intravenous thrombolysis (IVT) and randomized within 24 hours of last-known-well (LKW), resulting in a later-window population with prolonged duration of ischemia prior to reperfusion.

Scp776 showed a reasonable safety profile with directionally favorable effects on discharge NIHSS, final infarct volume (FIV), and 90-day modified Rankin Scale (mRS). We present longitudinal data analyses and treatment interactions across reperfusion timing and collateral status at presentation.

Analytic Framework

This poster expands the ARPEGGIO primary readout with **two layers of additional analyses**:

① **Longitudinal models** — recovery dynamics across clinical (NIHSS) and imaging (Infarct Volume, ASPECTS) endpoints. *Does scp776 alter the rates of neurologic recovery and infarct evolution?*

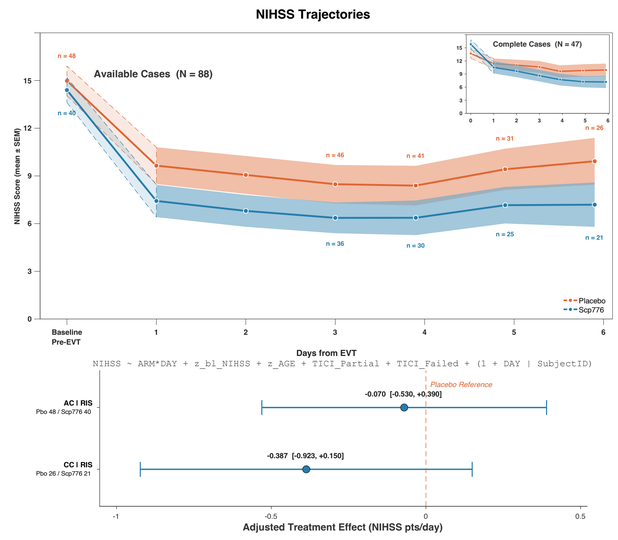
② **Heterogeneity of treatment effect (HTE) analyses** — pre-specified arm × covariate interactions on reperfusion timing and collateral status, plus exploratory subgroup follow-ons within each focal stratum. *Do scp776's directionally favorable signals concentrate where the apoptosis-targeting MoA predicts?*

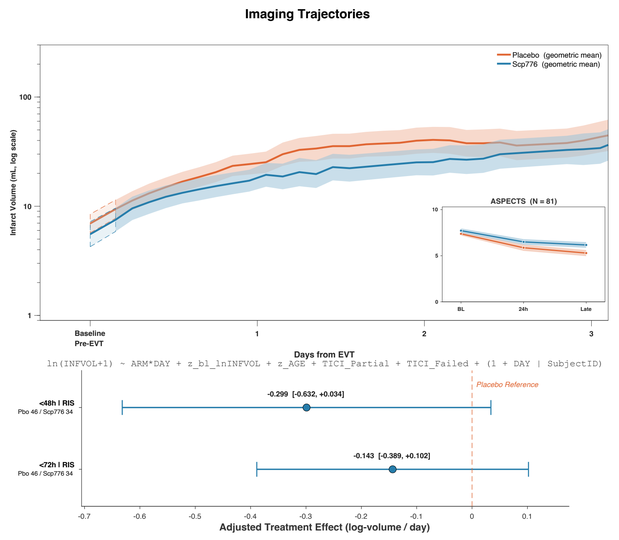
Analysis Population

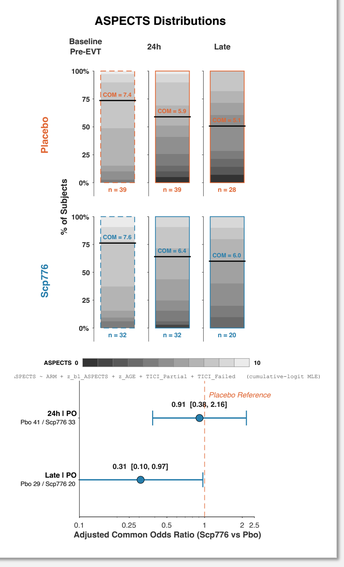
Baseline Characteristic	Placebo (n=48)	Scp776 (n=40)
Age (years)	71.5 [63.5-80.0]	72.0 [60.0-79.0]
Baseline NIHSS	14 [10-20]	16 [11-18]
Baseline ASPECTS	8 [7-8]	8 [7-9]
TICI grade	85% Full (>=2b)	85% Full (>=2b)
Collateral Status (Tan Grade ≥ 2)	92%	80%
Last-Known-Well to Reperfusion (hours)	11.8 [7.1-15.8]	10.2 [3.8-15.8]
Reperfusion to Drug (hours)	2.5 [1.8-3.6]	2.7 [2.0-3.5]
Baseline ln(Infarct Volume + 1)	2.09 [1.23-2.85]	1.68 [0.30-3.00]

All analyses presented are from the Per-Protocol Analysis Set — the primary contrast of placebo (n = 48) vs. the expanded scp776 dose level (n = 40), N = 88. Per-endpoint group sizes vary slightly by listwise deletion across required covariates. Directional findings are preserved in mITT sensitivity analyses.

① Exploratory Analyses of Longitudinal Clinical and Imaging Assessments

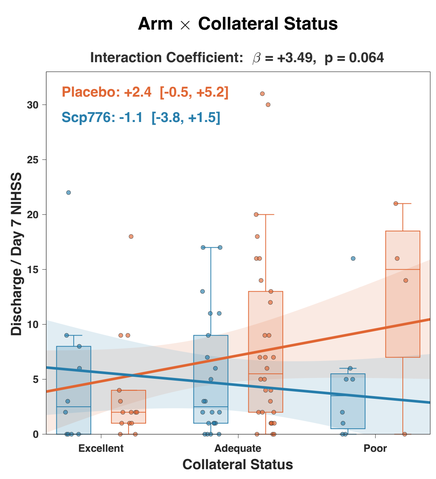


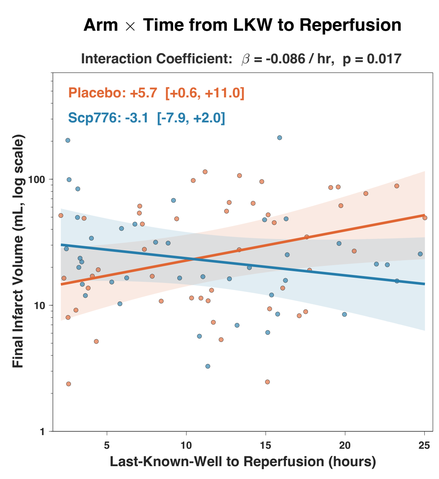




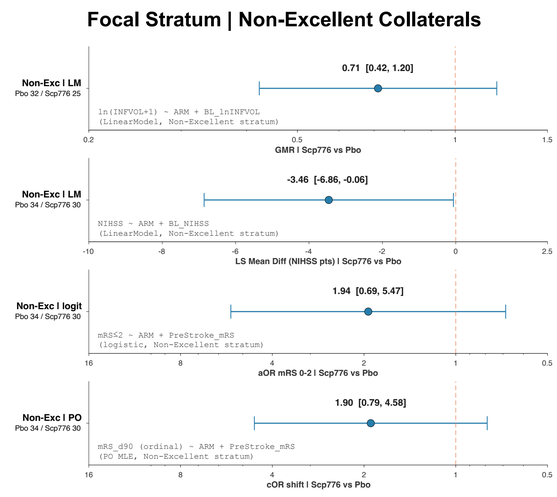
KEY METHODOLOGIC DETAILS: Pre-Specified Interaction Tests. SAP defined covariate set includes Age, Baseline NIHSS / ASPECTS, 6-level TICI grade. **Random-effects structure.** Random intercept + slope on time (RIS) used in linear mixed models. REML inference. **Exploratory Longitudinal Analyses.** Baseline outcome values are excluded from the modeled trajectory; they enter only as subject-level covariates. Including baseline as a modeled timepoint conflates pre-randomization state with on-treatment trajectory, biasing the arm × time slope estimate. Continuous covariates are z-scored within the analysis cohort. TICI3 collapse: success {2B, 2C, 3} = reference; partial {2A}; failed {<2a} pooled.

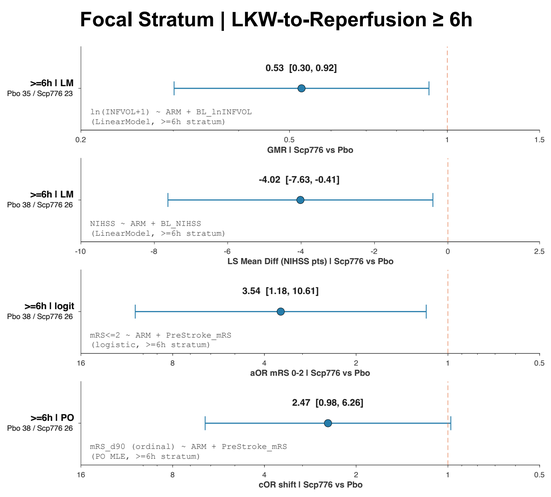
② Pre-Specified Arm × Covariate Interaction Tests





Exploratory Focal Stratum Subgroups





Findings ⟹ Concordant Signals & Caveats

Longitudinal models show concordant signals across endpoints.

- ✓ Scp776 shows directionally favorable acceleration in neurologic recovery.
- ✓ Scp776 shows directionally favorable reduction in per-day infarct growth.
- ✓ Scp776 shifts the late-timepoint ASPECTS distribution away from worse categories.

Pre-specified interaction tests align with scp776's apoptosis-targeting mechanism.

- ✓ Arm × Collateral Status on NIHSS shows *larger neurologic benefit as collateral support fails.*
- ✓ Arm × LKW2Rep on FIV shows *larger imaging benefit as ischemic exposure lengthens*.

Directional concordance across endpoints in populations anticipated to harbor greater apoptotic substrate.

- ➢ Within each interaction's focal stratum (Non-Excellent collaterals; ≥6h LKW), all four endpoints (FIV, NIHSS, mRS 0-2, mRS shift) favor scp776 with consistent direction.

Methodologic Limitations

Attrition is informative at both extremes of NIHSS. Rapid recoverers leave inpatient care sooner and severe cases (deaths, hemicraniectomies) are censored — producing missing-not-at-random (MNAR) attrition.

Longitudinal data analysis (LDA) in the acute phase has limited precedent. The SAP-specified MMRM was ill-suited to V2–V7 continuous visit timing and the MNAR attrition above; we pivoted to LMM RIS on continuous time with direct-likelihood handling of monotone dropout.

Subgroup analyses remain post-hoc despite pre-specified anchors. Exploratory subgroup forests anchor on pre-specified Arm × Covariate continuous-interaction tests (Collateral Status on NIHSS; LKW2Rep on FIV), but focal-stratum dichotomizations (≥6h LKW; Non-Excellent collaterals) are post-hoc. Baseline balance within subgroups maintained by SMD; endpoint concordance (FIV, NIHSS, mRS) used as internal-consistency check.

We extend our sincere gratitude to the ARPEGGIO investigators, study coordinators, patients, and families for their invaluable contributions to this research.

SILVER CREEK pharmaceuticals

Questions, please contact: info@silvercreekpharma.com

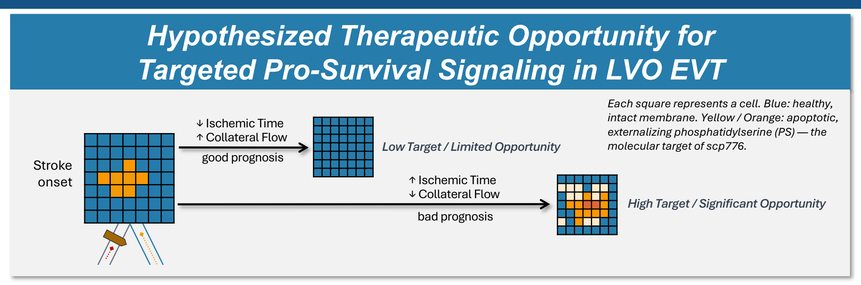
Disclosures:
KK, SP, and AS are employees of Silver Creek Pharmaceuticals, Inc. (SCP).
DL and EM report consulting fees from SCP.
SCP funded the ARPEGGIO study (NCT05585606).

Bridging Analytics to Mechanism ⟹ Proposed Model of Scp776 Benefit

In pre-specified assessments of heterogeneity, treatment interactions were observed in directions consistent with scp776's targeting of apoptotic cells and tissue.

> On the tissue endpoint (FIV), the interaction between treatment and time from LKW to reperfusion was statistically significant (p=0.017, PPAS), indicating that scp776's effect on **infarct reduction increases with longer ischemic exposure**.
>
> On the clinical endpoint (Discharge / Day 7 NIHSS), the treatment effect was modified by collateral status (interaction p=0.064, PPAS), with the **largest neurologic benefit observed in patients with poor collateral circulation**.

These interactions are interpreted as consistent with larger treatment effects in the ARPEGGIO participants *anticipated to harbor* greater apoptotic substrate available for rescue. These exploratory findings warrant prospective evaluation and may have implications for patient selection in future trials.



Active Rescue

Scp776 acts not by directly inhibiting injury pathways but by **activating IGF-1-mediated pro-survival signaling on cells that have entered apoptosis**. Activator approaches may have less temporal urgency than injury-pathway inhibitors and may deliver greatest *relative* benefit after reperfusion where ischemic burden is greatest.