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Exploratory Biomarker and Imaging Outcome Signals in the Singaporean Trial of CN-105 Treatment for Acute Supratentorial Intracerebral Hemorrhage (S-CATCH)

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Exploratory Biomarker and Imaging Outcome Signals in Singaporean Trial of CN-105 Treatment for Acute Supratentorial Intracerebral Hemorrhage (S-CATCH)

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Compliance with instructions to authors

The manuscript has been prepared in accordance with the Instructions for Authors for *Neurocritical Care*.

Individual author contributions

Conceptualization and study design: Daniel T. Laskowitz, Peter G. Kranz, and Michael L. James.

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Data analysis and statistical interpretation: Samuel Teshome, Liam O'Hara, Ashley Lin, Cina Sasannejad, and Michael L. James.

Data interpretation: all authors.

Manuscript drafting: Samuel Teshome, Ashley Lin, and Michael L. James.

All authors critically revised the manuscript for important intellectual content and reviewed and approved the final manuscript.

Authorship requirements and final manuscript approval

All authors meet the International Committee of Medical Journal Editors authorship criteria. Each author made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; participated in drafting the manuscript or critically revising it for important intellectual content; approved the final version; and agrees to be accountable for all aspects of the work, including ensuring that questions concerning its accuracy or integrity are appropriately investigated and resolved.

Previous publication and exclusive submission

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The parent S-CATCH trial's safety and functional-outcome findings were previously published in *Neurocritical Care* by Cheong and colleagues in 2026 (doi:10.1007/s12028-026-02563-7). The present manuscript reports an exploratory secondary analysis of plasma biomarkers and imaging measures from the same trial cohort. The relationship to the parent trial report is identified in the manuscript.

Ethical approval and informed consent

The S-CATCH trial was approved by the SingHealth Centralised Institutional Review Board. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. Written informed consent was obtained from all participants or their legally authorized representatives.

The trial was registered at ClinicalTrials.gov under NCT03711903 on October 16, 2018.

Conflicts of interest

Daniel T. Laskowitz and Maureen Maughan are affiliated with AegisCN, LLC, which holds licensing rights to CN-105.

Samuel Teshome, Ashley Lin, Tien Meng Cheong, Cina Sasannejad, Liam O'Hara, Nicolas Kon Kam King, Vincent Yew Poh Ng, Saheen Nehar, Fatimah Misbaah Abdul Rahim, Peter G. Kranz, and Michael L. James declare no competing interests.

Reporting checklist

The completed checklist is included at the end of the manuscript. Analyses reported in this manuscript are identified as exploratory secondary analyses of the S-CATCH randomized trial.

Artificial intelligence disclosure

OpenAI Codex was used to assist with literature searches, editorial suggestions, preparation of reporting checklists and a participant-flow diagram, and cross-checking reported methods and results against study documents. The authors reviewed and verified the AI-assisted content and take full responsibility for the accuracy, integrity, and originality of the submitted work.

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Abstract

Background/Objective: CN-105 is an apolipoprotein E-mimetic pentapeptide designed to attenuate neuroinflammation after intracerebral hemorrhage (ICH). This exploratory secondary analysis of the Singaporean Trial of CN-105 Treatment for Acute Supratentorial Intracerebral Hemorrhage (S-CATCH) evaluated plasma and imaging biomarkers in relation to functional outcome and treatment response.

Methods: S-CATCH was a randomized, double-blind, placebo-controlled phase 2b trial of CN-105 in 60 patients with acute primary supratentorial ICH. Serial plasma protein concentrations and computed tomography measurements were evaluated for associations with 30- and 90-day modified Rankin Scale outcomes. Treatment-associated trajectories were expressed as CN-105:placebo ratios of geometric mean fold changes from baseline. Perihematomal edema was evaluated using the edema:blood volume (E:BV) ratio.

Results: Higher interleukin-6, D-dimer, C-reactive protein, S100 calcium-binding protein B, and B-type natriuretic peptide concentrations were associated with worse functional outcomes in unadjusted analyses. CN-105 was associated with smaller geometric mean fold changes in D-dimer on day 1 (ratio 0.644; $p = 0.042$) and vascular endothelial growth factor on day 2 (ratio 0.777; $p = 0.012$). Overall imaging models containing baseline D-dimer, tumor necrosis factor-α, or vascular endothelial growth factor, treatment arm, and their interaction were significant on individual scan days. P-values were not adjusted for multiple comparisons.

Conclusions: CN-105 was not significantly associated with functional outcome. D-dimer showed exploratory outcome- and treatment-associated signals warranting further validation as a candidate prognostic and pharmacodynamic marker.

Keywords: CN-105; apolipoprotein E mimetic peptide; neuroinflammation; perihematomal edema; plasma protein biomarkers; Clinical trial

Clinical Trial Registration: ClinicalTrials.gov, NCT03711903. Registered October 16, 2018. https://clinicaltrials.gov/study/NCT03711903?term=NCT03711903&rank=1

Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 10% of strokes in the United States and remains the most devastating subtype with 30-day mortality exceeding 40% and fewer than 20% of survivors achieving functional independence[1]. ICH-related brain injury is mediated through both direct mechanical effects, i.e., hematoma formation and expansion, and secondary pathophysiological processes, i.e., disruption of the blood-brain barrier, heme degradation, and perihematomal edema (PHE) formation[2]. Thus, coagulation and neuroinflammatory processes likely represent promising therapeutic targets.

Plasma coagulation and inflammatory proteins have previously been associated with ICH severity and outcome[3–5]. Elevated plasma D-dimer, a fibrin degradation product in coagulation and fibrinolytic activation, occurs early after ICH and has been associated with early neurological deterioration, mortality, and worse neurological outcomes[4,6–8]. Similarly, interleukin-6 (IL-6), a key mediator of neuroinflammatory cascade, peaks early after ICH and correlates with hematoma and PHE volume[5,9]. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that participates in the early neuroinflammatory cascade[10], contributes directly to PHE formation[11], and predicts functional status and 3-month neurological outcome[12]. Thus, certain plasma proteins may reflect evolving pathophysiology that affects ultimate neurological outcome after ICH, making them suitable for development of potential therapeutics.

CN-105, a five amino-acid peptide derived from the receptor-binding region of apolipoprotein E (apoE), represents a novel therapeutic approach to treating acute ICH[13,14]. While pleotropic, one salient mechanism for limiting neuroinflammation is endogenous apoE activation of low density lipoprotein receptor-related protein 1 (LRP1), but this response is

constrained after ICH because the intact holoprotein does not readily cross the blood-brain barrier[13]. CN-105 was specifically designed to mimic apoE-LRP1 receptor interactions to mediate anti-inflammatory and neuroprotective signaling cascades[15–20]. Preclinical studies of ICH and other acute brain injury states have repeatedly shown that CN-105 improves histological and neurological outcomes[13,19,21–23]. Early-phase clinical trials have demonstrated safety, predictable pharmacokinetics, and positive signals of neurological improvement at 30 days in patients with acute ICH[14,16]. The CN-105 in Participants with Acute Supratentorial Intracerebral Hemorrhage Trial in Singapore (S-CATCH) trial confirmed CN-105's safety profile and feasibility from US trials, but was not powered for efficacy[14,16,24].

Relationships between treatment, plasma proteins, imaging, and neurological outcomes for the S-CATCH cohort have not been previously characterized. This post-hoc exploratory analysis of the S-CATCH trial aims to evaluate these potential associations and explore whether CN-105 treatment modifies these biological signals.

Materials and Methods

Study Design and Patient population

The S-CATCH trial (Clinical trial number: NCT03711903) was a randomized Phase 2b, double-blind, and placebo-controlled study of CN-105 peptide as a treatment for patients with acute primary supratentorial ICH. Regulated by Health Sciences Authority of Singapore, the study protocol, including informed consent, was reviewed and approved by the SingHealth Institutional Review Board. This clinical trial was conducted between March 2019 and June 2022 in accordance with the Declaration of Helsinki, International Conference for Harmonization Good Clinical Practice (ICH-GCP) and local regulations. All participants or their

legally authorized representatives provided written informed consent. A total of 60 participants were enrolled in the study from the National Neuroscience Institute, Singapore (30 in placebo arm, 30 in CN-105 treatment arm). Participants were eligible if they were between the ages of 30 to 80, and if they had a confirmed radiographic diagnosis of spontaneous supratentorial ICH. Additional inclusion criteria were the ability to administer the first dose of study treatment within 12 hours of ICH symptom onset, an intraparenchymal hematoma on an interpretable brain computed tomography (CT) scan, a Glasgow Coma Scale (GCS) score ≥5, a National Institutes of Health Stroke Scale (NIHSS) score ≥4, and systolic blood pressure <200 mmHg at enrollment. Individuals were excluded from the study if they had infratentorial or primary intraventricular hemorrhage, were pregnant or lactating, had ICH due to secondary causes or extra-axial hemorrhage that limited recovery potential, were determined by study investigator to be at high risk for obstructive hydrocephalus, had active herniation symptoms, or platelet count less than 100,000/μL. All patients, legally authorized representatives, treatment teams, and study personnel were blinded to the treatment allocation.

Intervention and Outcome Measures

After eligibility assessment, written informed consent, and randomization, participants received intravenous CN-105 at 1.0 mg/kg or a matching volume of normal saline within 12 hours of symptom onset and every 6 hours thereafter for 3 days. All participants received standard-of-care treatment for ICH based on the 2022 American Heart Association guidelines[1]. The decision to perform decompressive surgery for neurological deterioration was based on the individual treating physician, who remained blinded to treatment allocation.

Blood samples were collected at enrollment immediately before the first dose of study treatment (pre-treatment, day 0) and subsequently at 24 ± 8-hour intervals through day 5. Blood

samples were centrifuged within 1 hour of collection at 2000 × g for 10 minutes, preferentially at 4°C, to separate cellular components. Plasma was aliquoted into labeled cryotubes in 1 mL aliquots, and stored at −20°C or colder until analysis. S100B, matrix metalloproteinase (MMP)-3, MMP-9, C-reactive protein (CRP), D-dimer, B-type natriuretic peptide (BNP), IL-6, TNF-α, and vascular endothelial growth factor (VEGF) were measured from each sample.

Clinical CT imaging was performed at recruitment (Day 0), with follow-up scans obtained on Days 1, 2, and 5. CT imaging utilized a standardized protocol on identical Discovery CT750 HD scanners (GE Healthcare) to minimize inter-scanner variability. Thin contiguous axial nonhelical images were acquired from the vertex to the foramen magnum using a detector configuration generating 1.25 mm slices at 512 × 512 matrix resolution, 120 kVp tube voltage, and 335 mAs tube current. Raw 1.25 mm datasets were reconstructed into 5 mm slices for routine clinical interpretation. Serial CT scans for each participant were co-registered to the baseline scan using osseous craniofacial landmarks to account for differences in positioning and slice angulation. De-identified Digital Imaging and Communications in Medicine (DICOM) datasets were processed offline for volumetric quantification of PHE and intraparenchymal hemorrhage. Hematoma and PHE volumes were quantified by semiautomated segmentation performed by a neuroradiologist (PGK) using AnalyzePro version 1.0 and previously published methods[25].

Functional status was assessed using the modified Rankin Scale (mRS) daily for the first 5 days after enrollment and at outpatient follow-up visits on days 30 and 90 (±7 days). Premorbid mRS score was recorded at enrollment. All study personnel involved in enrollment, treatment, and assessment were blinded to treatment allocation, and the study remained blinded

until database lock of the final analysis. 90-day mRS was dichotomized as 0–3 (favorable) versus 4–6 (unfavorable) on the basis of ability to ambulate independently. Three participants were excluded from mRS analyses because their premorbid mRS was ≥3. Available mRS outcomes comprised 56 participants at Day 30 and 57 at Day 90.

Statistical Analysis

All analyses were conducted in R version 4.4.1,using modified Rankin Scale (mRS) score, plasma protein concentration, hematoma volume, and PHE volume data from the S-CATCH trialThree participants were excluded from mRS summaries and analyses because their premorbid mRS scores were ≥3. One participant's day 5 scan was flagged as a possible outlier because of interval hemicraniectomy and possible hematoma evacuation but was retained in the analysis. MMP-3 and MMP-9 were excluded from the initial ordinal outcome analyses because the first 10 participants could not be included for these biomarkers. Glial fibrillary acidic protein was excluded from summaries and analyses because many measurements were below the lower limit of quantification.

Neurological outcome was analyzed using two complementary approaches. For ordinal analyses, a Wilcoxon shift test was used, following the approach described in prior stroke literature[26], with mRS categories 5 and 6 combined into a single category. For dichotomized analyses, mRS was classified as favorable versus unfavorable using two cut points: 0–2 versus 3–6, consistent with the primary outcome definition, and 0–3 versus 4–6. Logistic regression models were fit to estimate odds ratios (ORs), 95% confidence intervals, and p-values for the association between treatment assignment and neurological outcome. P-values in this analysis were not adjusted for false discovery rate or familywise error rate.

Exploratory ordinal logistic regression analyses evaluated one-, two-, and three-protein combinations of BNP, CRP, D-dimer, IL-6, S100B, TNF-α, and VEGF across measurement days. Candidate models included protein main effects and pairwise interactions and were compared using the corrected Akaike information criterion (AICc). Separately, receiver operating characteristic analyses evaluated discrimination of dichotomized 90-day mRS (0–3 versus 4–6) using individual proteins and selected protein combinations, including pre-treatment measurements and post-treatment averages. The reported discrimination reflects performance in the analyzed sample and does not establish performance in independent patients.

Treatment-associated plasma protein trajectories were assessed using longitudinal mixed-effects models with participant as a random effect and treatment arm, visit, and their interaction as fixed effects. The dependent variable was the log-transformed post-treatment concentration minus the log-transformed pre-treatment concentration. Back-transformed between-group contrasts were expressed as CN-105:placebo ratios of geometric mean fold changes from baseline, with 95% confidence intervals. A ratio below 1 indicates a smaller fold change in the CN-105 group, which may reflect a smaller increase or a greater decrease.

To assess whether baseline inflammatory state altered the relationship between CN-105 and outcome, ordinal logistic models were fit with mRS as the dependent variable and log-transformed pre-treatment plasma protein, treatment arm, and their interaction as predictors. The initial model took the form mRS ~ log(pre-treatment plasma protein) + arm + log(pre-treatment plasma protein) × arm. When the plasma protein-by-treatment interaction was not

significant, the model was simplified to include only pre-treatment plasma protein and treatment arm main effects.

The edema:blood volume (E:BV) ratio, calculated as PHE volume divided by hematoma volume, was the primary imaging biomarker.Two related modeling strategies were used. First, for each imaging scan day, linear models were fit using log-transformed E:BV ratio as the dependent variable and log-transformed pre-treatment plasma protein concentration, treatment arm, and their interaction as predictors: log(E:BV ratio) ~ log(pre-treatment plasma protein) + arm + log(pre-treatment plasma protein) × arm. Pre-treatment plasma protein concentrations were included as covariates because of their observed associations with mRS; R^2 values and p-values are reported for the overall models rather than individual coefficients. Second, to assess whether PHE added explanatory value beyond pre-treatment plasma protein concentration, logistic regression models were fit with dichotomized mRS as the dependent variable and log-transformed E:BV ratio and log-transformed pre-treatment plasma protein concentration as predictors. These models were fit for both binary outcome definitions, mRS 0–2 versus 3–6 and mRS 0–3 versus 4–6, at both 30 and 90 days.

OpenAI Codex was used to assist with literature searches, editorial suggestions, preparation of reporting checklists and a participant-flow diagram, and cross-checking reported methods and results against study documents. The authors reviewed and verified the AI-assisted content and take full responsibility for the accuracy, integrity, and originality of the submitted work.

Results

Plasma protein associations with 90-day mRS

The association between plasma protein concentrations and functional outcome 90 days post ICH as measured by modified rankin score (mRS) was evaluated in figure 1. Concentration curves of measured plasma proteins were stratified by mRS over the 5 days of sampling (Figure 1). Odds ratios from univariate proportional-odds ordinal logistic regression models were used to relate each log-transformed plasma protein concentration from each sampling day to 90-day mRS (Figure 2). CRP, BNP and IL-6 showed the most consistent associations with worse 90-day mRS across all sampling days.

Models incorporating combinations of plasma proteins were systematically evaluated to determine whether they improved characterization of 90-day mRS outcomes compared with single-protein models. Two-protein combinations showed only modest incremental improvement in ordinal model fit, and three-protein models provided no clear additional value over individual proteins. In the separate ROC analysis, the best-performing combination model incorporated post-treatment average BNP and pre-treatment IL-6 concentrations. This combination provided higher discrimination than the strongest single-protein model, which used post-treatment average CRP (Figure 3). Given the risk of overfitting and uncertain generalizability, systematic evaluation of plasma protein combinations did not establish a robust multi-protein prediction model.

Plasma protein concentrations and CN-105 treatment

We next evaluated associations between plasma protein concentrations and CN-105 treatment. After adjustment for pre-treatment protein concentrations, geometric mean ratios were used to examine whether CN-105 treatment was associated with daily changes in plasma protein concentrations over the first 5 days after ICH (Figure 4). While not corrected for multiple comparisons, two statistically significant treatment-associated reductions were observed: Day 1 D-dimer (CN-105:placebo ratio 0.644; 95% CI 0.421–0.983; p = 0.042) and Day 2 VEGF (CN-105:placebo ratio 0.777; 95% CI 0.638–0.944; p = 0.012). Interesting directional trends included IL-6 with a nonsignificant decrease and BNP with a nonsignificant upward shift in the CN-105:placebo ratio over the sampling days. Despite the lack of associations, treatment effect of CN-105 on mRS was assessed. In analyses of individual proteins (Figure 2), pre-treatment concentrations were associated with 90-day mRS as strong or stronger than any other day's sampling for every protein measured. Thus, interaction terms between pre-treatment plasma protein concentration and treatment arm were tested for association with 90-day mRS for each protein (Figure 5). No statistical associations could be found for any protein's interaction with CN-105.

Plasma protein and PHE associations with 90-day mRS

Hematoma volume was relatively stable across all imaging days, but edema volume increased 3 fold from baseline to day 5 (Supplemental Figure 1); thus, edema-to-blood volume (E:BV) ratio changes were driven largely by edema expansion. Treatment-related differences in E:BV ratio were not uniform across mRS strata and were most apparent among participants with an mRS score of 5 (Figure 6). This observation was exploratory and not sufficient to establish a subgroup-specific treatment response.

We then tested whether the E:BV ratio added additional weight to associations with mRS beyond pre-treatment plasma protein concentrations alone. In models containing both pre-treatment plasma protein concentration and E:BV ratio, E:BV ratio associations were non-significant (Supplemental Table 1). In these models, notably, BNP, D-dimer, IL-6, and S100B showed significant plasma protein terms at every imaging day. These findings suggest that pre-treatment plasma protein concentrations carried more consistent outcome-related information than the E:BV ratio in this cohort.

To evaluate whether cerebral edema was associated with CN-105 treatment, models incorporating pre-treatment plasma protein concentration, treatment arm, and their interaction were used to model log-transformed E:BV ratio for each imaging day (Table 1). In this framework, p-values reflect overall model significance rather than individual plasma proteins, CN-105 treatment, or interaction terms. While overall model significance was found for D-dimer, TNF-α, and VEGF on specific single imaging days, R^2 values were low and significance was not sustained across multiple imaging days for any protein.

Discussion

The aim of this secondary analysis of the S-CATCH trial was to explore associations of plasma protein and radiographic biomarkers with CN-105 treatment effect and durable neurological outcome[24]. While exploratory in nature, our analyses suggest CN-105 may influence certain plasma proteins related to post-ICH outcome, consistent with prior findings from the US-based CATCH trial showing that CN-105 may attenuate secondary injury, neuroinflammation, and edema[25,27–29]. The present study found evidence that S100B, IL-6, D-dimer, CRP, and BNP concentrations may be related to mRS at 30 and 90 days after ICH.

However perihematomal edema (PHE) radiographic markers added little information about 90-day functional outcome beyond baseline plasma protein concentrations, and CN-105 treatment was not significantly associated with improved neurological outcome. The protein-PHE association reported in the CATCH pilot analysis were not replicated[25,30].

Pre-treatment inflammatory and acute phase plasma protein concentrations were associated with post-ICH neurological outcome in this cohort, while CN-105 treatment associated influence on plasma proteins did not affect functional outcomes. This suggest that post-ICH inflammatory state is the main predictor of functional recovery, overwhelming any post-treatment inflammatory signal. Pre-treatment S100B, IL-6, D-dimer, CRP, and BNP were all associated with worse neurological outcome and appeared to drive all associations in subsequent modeling (i.e., multiple proteins, treatment arms, PHE, etc.). These findings suggest initial inflammatory state after injury, rather than CN-105 treatment or edema generation, impacts functional outcome[29,31–33], and all these proteins have sufficient biological plausibility to be related to injury severity and repair[5,34–36].

In this cohort, higher D-dimer, particularly pre-treatment concentration, was most consistently significant across various models: univariate association with 90-day mRS, early CN-105 treatment associated reduction in concentration, and associations with PHE. These findings support further investigation of D-dimer as a candidate prognostic and pharmacodynamic marker. This interpretation is consistent with prior studies linking elevated D-dimer to poor neurological outcome, early neurologic deterioration, mortality, and larger hemorrhage burden[4,7,29,31]. Elevated D-dimer likely reflects the local hemostatic response to hematoma formation, including fibrin deposition and fibrinolysis[37].

Perihematomal edema develops within hours after ICH, evolves over days to weeks, and is associated with worse outcomes[27,29]. In our analysis hematoma volume was relatively stable over the 5 days of imaging, while PHE increased, consistent with prior reports[38]. Due to the strength of associations between pre-treatment plasma protein concentrations and mRS, adding PHE to these models contributed little. Thus, future study may seek to define biologically plausible linkages between post-ICH plasma proteins changes and PHE in a larger cohort. As an example, prior studies have shown higher VEGF level at 72 hours after ICH is associated with favorable 3-month outcome, neurologic improvement, and reduced residual lesion volume, supporting a possible reparative role for VEGF[39]. Further, future work should consider use of other PHE measurements to further define any possible relationships, including edema extension distance, which may better isolate edema biology from hematoma volume than absolute or relative PHE measures[40].

Taken together, these findings suggest a small set of candidate markers might be deployed in a definitive trial. Previous studies have shown D-Dimer and CRP are biomarkers that add valuable information to composite ICH risk scores, and are measurable on admission using routine clinical assays[3,35]. However, no treatment-related effects on these biomarkers have been found[5]. In fact, the U.S. based CATCH trial biomarker analyses only examined protein associations with perihematomal edema[30]. S-CATCH extends that work by providing, to our knowledge, the first randomized, placebo-controlled estimates of apoE-mimetic peptide effects on plasma protein biomarkers in acute ICH. Of these, D-dimer was most consistently associated with outcome and seemingly responsive to CN-105 treatment. Prospective validation is needed to determine whether treatment-associated changes in D-dimer are related to longer-term functional outcome. Future trials should test whether pre-treatment D-dimer identifies patients

morelikely to benefit from CN-105, using denser sampling across the interval in which treatment-associated differences were observed, prespecified pharmacodynamic endpoints, and standardized serial imaging.

Limitations and Future Directions

Given the exploratory nature of this secondary analysis of a Phase 2b trial our current results should be interpreted cautiously. In particular, limitations include small sample size, no significant treatment effect on neurological outcome, and no correction for multiple comparisons. The sample size's limited power for plasma protein and imaging sub analyses, prevented confident estimation of individual treatment-by-biomarker interactions, and constrained interpretation of subgroup patterns observed on descriptive plots. In addition, because this analysis focused on intermediate plasma and radiographic correlates rather than definitive clinical efficacy endpoints, it cannot determine whether the observed biological signals translate into meaningful patient-level benefit. These limitations are especially relevant given that candidate markers require external validation, replication in independent cohorts, and integration into multivariable models before clinical use. Future trials must prospectively incorporate appropriately powered samples with serial biomarker sampling, standardized imaging, and prespecified biomarker-response analyses to test whether markers such as D-dimer, TNF-α, and IL-6 identify treatment-responsive subgroups and function as pharmacodynamic indicators of interventions designed to reduce neuroinflammation after ICH such as CN-105.

Conclusion

In this secondary analysis of S-CATCH, biologically plausible plasma proteins were associated with long-term neurological outcome after ICH and may demonstrate relationships between brain edema and CN-105 treatment. Similar to prior work, this supports CN-105 modification of inflammatory and coagulation pathways rather than direct effects on hematoma-related injury[13,21,41]. However, these protein and imaging biomarker findings should only be interpreted as hypothesis-generating and guide design of future studies of biomarker validation and CN-105 efficacy.

Figures

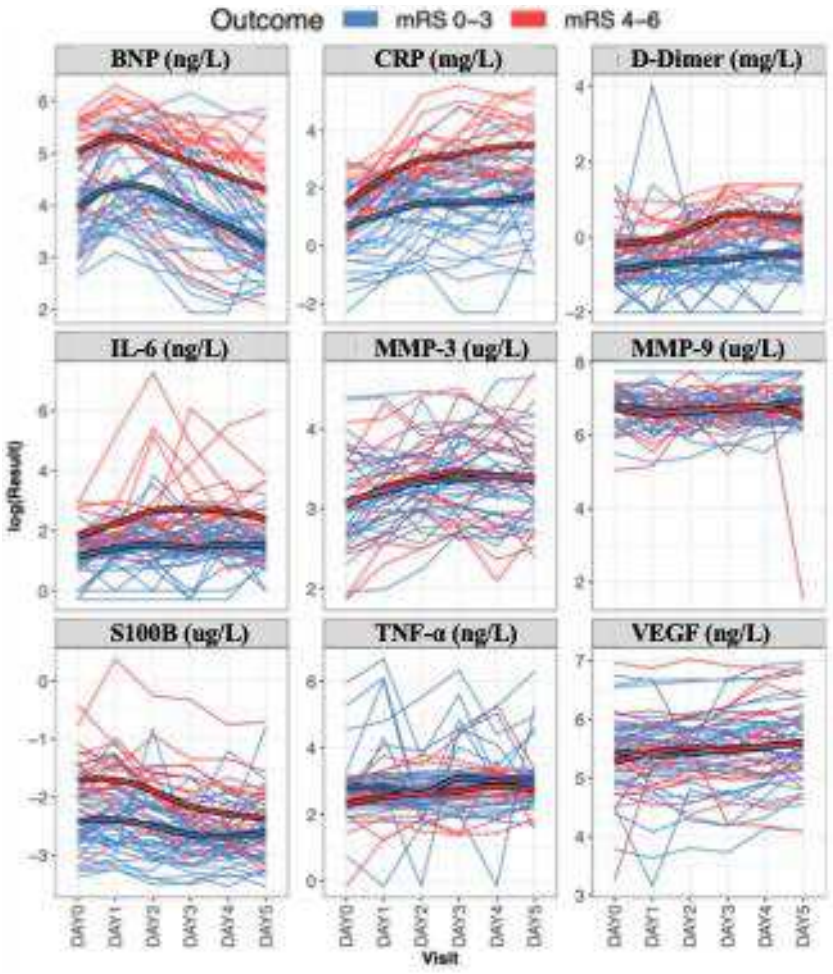


Fig 1. Plasma protein concentrations across sampling days by 90-day functional outcome. Log-transformed plasma protein concentrations are shown for each of the nine measured proteins across study Days 0 to 5 in participants with acute supratentorial intracerebral hemorrhage (ICH) enrolled in the S-CATCH trial (n = 57, after exclusion of 3 participants with a premorbid modified Rankin Scale [mRS] score of 3 or greater). Day 0 samples were obtained immediately before the first dose of study drug (pre-treatment). Thin lines represent individual participants, and thick smoothed curves represent group trends. Blue denotes favorable 90-day outcome (mRS 0–3) and red denotes unfavorable 90-day outcome (mRS 4–6). B-type natriuretic peptide (BNP), C-reactive protein (CRP), D-dimer, interleukin-6 (IL-6), and S100B were higher among participants with unfavorable 90-day outcome across multiple sampling days, whereas tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-3, and MMP-9 showed less consistent differences. Both treatment arms are pooled in this figure.

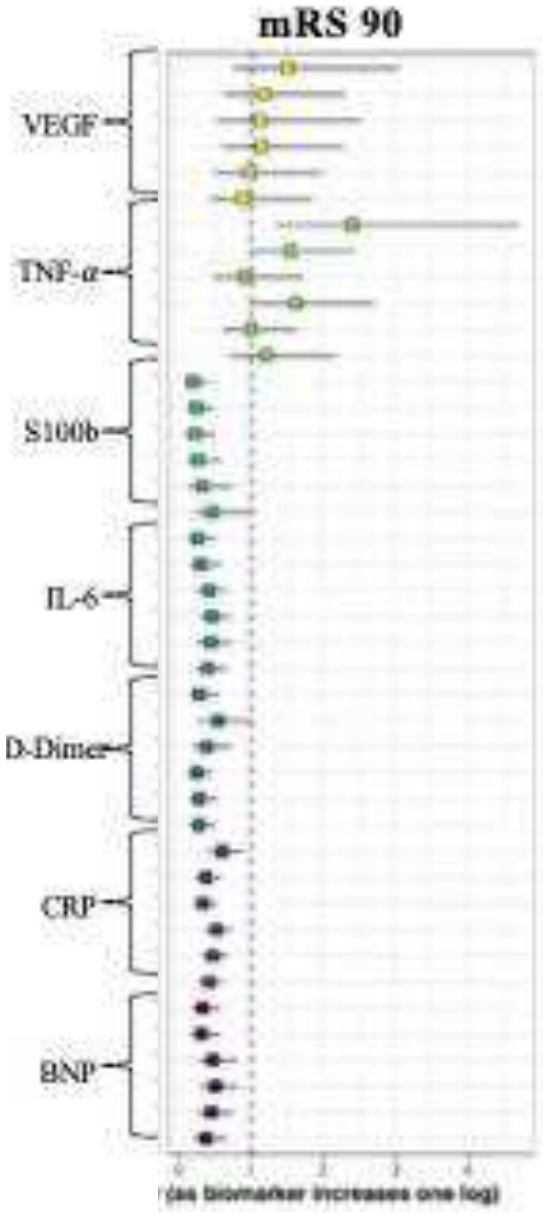


Fig 2. Univariate associations between plasma protein concentrations and functional outcome. Forest plots show odds ratios (ORs) from univariate proportional-odds ordinal logistic regression models relating each log-transformed plasma protein concentration to modified Rankin Scale (mRS) score in participants with acute supratentorial intracerebral hemorrhage enrolled in the S-CATCH trial (n = 56 at 30 days and n=57 at day 90). Each row represents one plasma protein measured on one study day, from Day 0 (pre-treatment) through Day 5. Points represent estimated ORs and horizontal bars represent 95% confidence intervals; the vertical reference line marks an OR of 1.0. An OR below 1.0 indicates that a higher plasma protein concentration was associated with worse neurological outcome, and an OR above 1.0 indicates that a higher concentration was associated with better outcome. Results are shown separately for mRS at 30 days and mRS at 90 days. Higher S100B, interleukin-6, D-dimer, C-reactive protein, and B-type natriuretic peptide concentrations were associated with worse functional outcome

(OR < 1.0). Models are unadjusted and pool both treatment arms; p-values are not corrected for multiple comparisons.

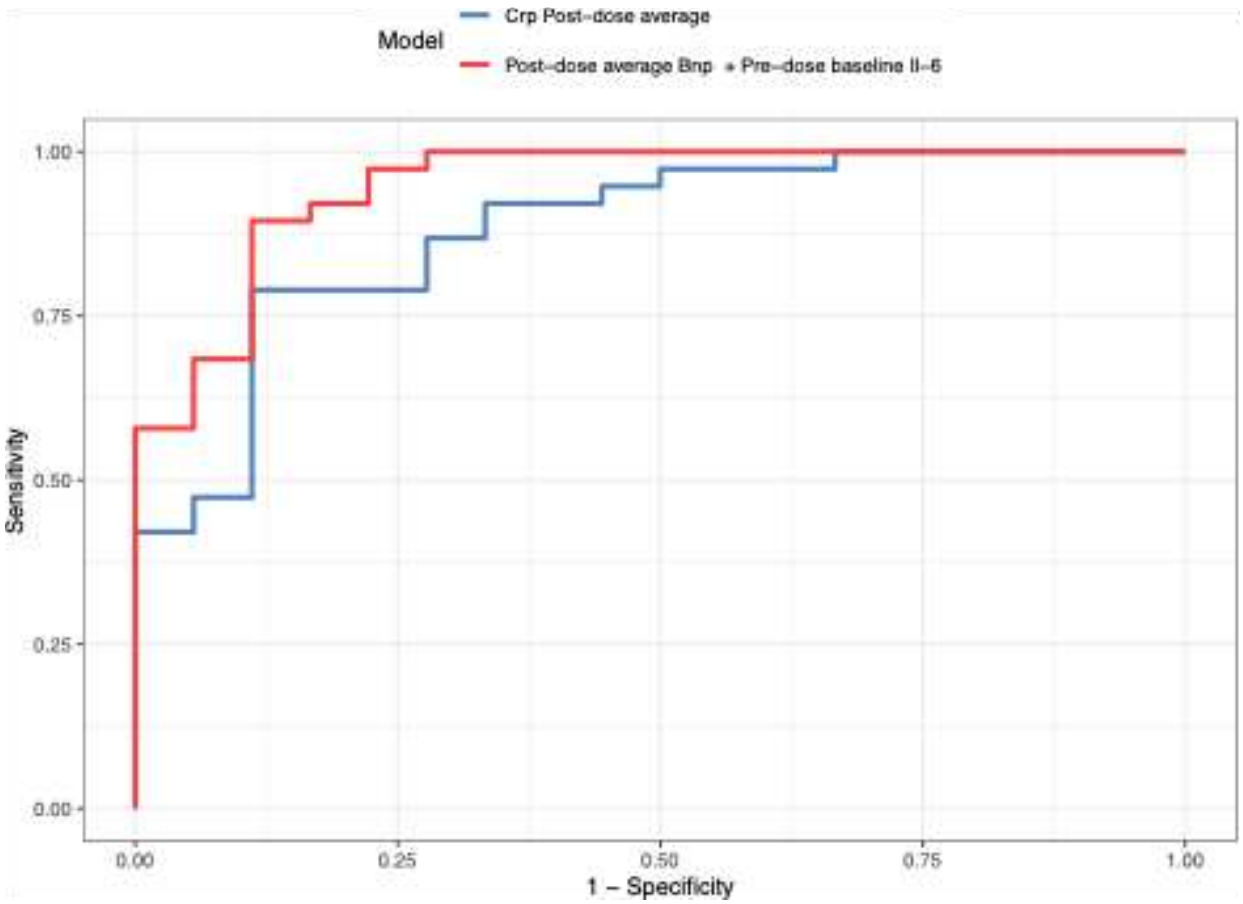


Fig 3. Receiver operating characteristic curves for selected single- and multi-protein models of 90-day functional outcome. Receiver operating characteristic (ROC) curves are shown for logistic models of dichotomized 90-day modified Rankin Scale (mRS) outcome in participants with acute supratentorial intracerebral hemorrhage enrolled in the S-CATCH trial (n = 57). Blue denotes a selected single-protein model, based on post-treatment average C-reactive protein (CRP). Red denotes the best-performing exploratory two-protein model, incorporating post-treatment average B-type natriuretic peptide (BNP) and pre-treatment interleukin-6 (IL-6). Post-treatment average denotes the mean of Day 1 through Day 5 measurements; pre-treatment denotes the Day 0 sample obtained before the first dose of study drug. The two-protein model showed higher apparent discrimination than CRP alone; however, this comparison was exploratory, the model was selected after evaluating all one-, two-, and three-protein combinations, and the difference may reflect overfitting rather than a generalizable improvement in outcome prediction.

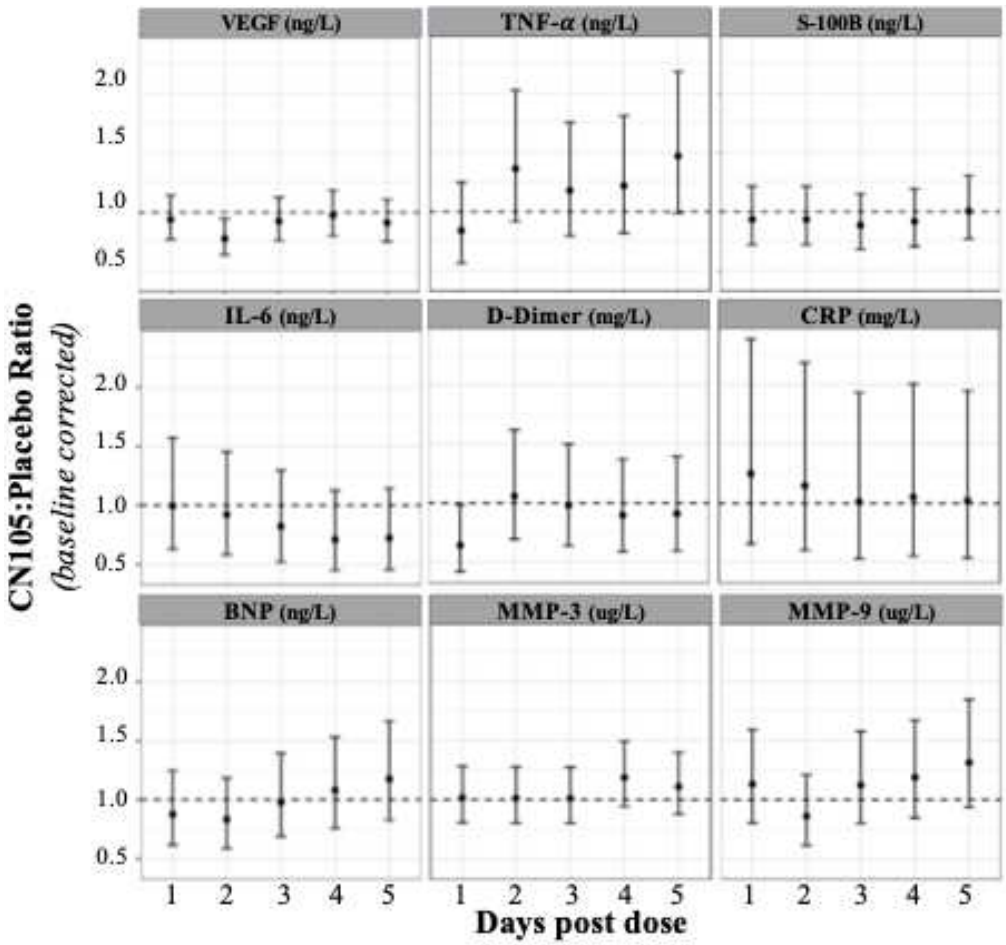


Fig 4. Treatment-associated changes in plasma protein concentrations over time. CN-105:placebo ratios of geometric mean fold changes from pre-treatment plasma protein concentrations are shown in participants with acute supratentorial intracerebral hemorrhage enrolled in the S-CATCH trial (n = 57). Vertical bars represent 95% confidence intervals and the dashed horizontal line marks a ratio of 1.0, indicating no difference between treatment groups. A ratio below 1.0 indicates a smaller fold change from baseline in plasma protein concentration in the CN-105 group than in the placebo group. Statistically significant differences were observed for D-dimer on Day 1 (ratio 0.644; 95% CI 0.421–0.983; p = 0.042) and vascular endothelial growth factor on Day 2 (ratio 0.777; 95% CI 0.638–0.944; p = 0.012). p-values are not corrected for multiple comparisons.

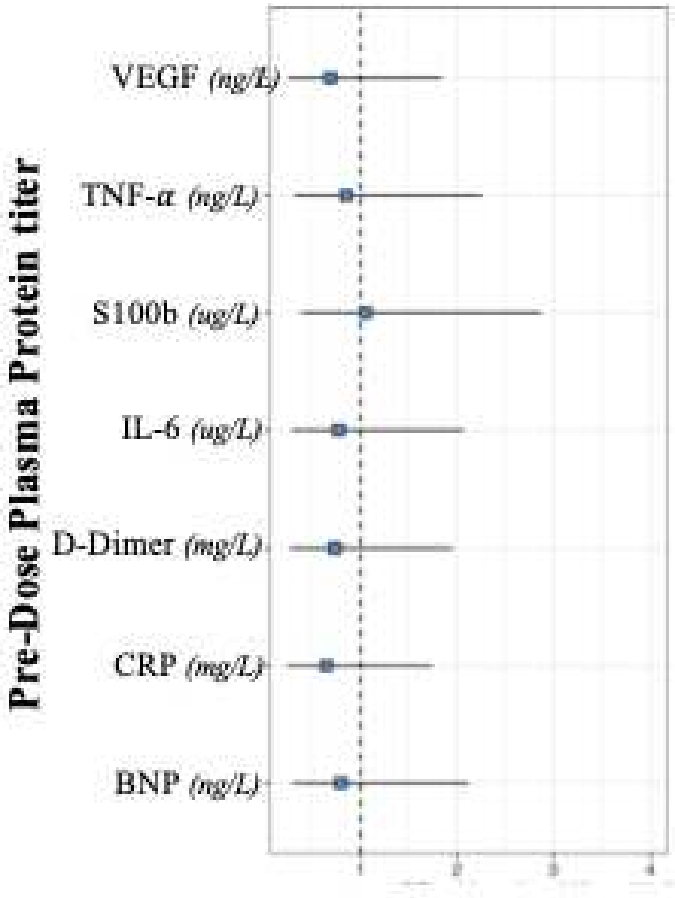


Fig 5. CN-105 treatment associations with 90-day functional outcome after adjustment for pre-treatment plasma proteins. Each row shows the CN-105-versus-placebo odds ratio from a separate ordinal logistic regression model containing treatment arm and one log-transformed Day 0 plasma protein concentration. Horizontal bars represent 95% confidence intervals, and the reference line indicates an odds ratio of 1. Confidence intervals for the treatment effect include 1 in all models. These estimates do not represent the effects of the plasma protein covariates. P-values were not adjusted for multiple comparisons.

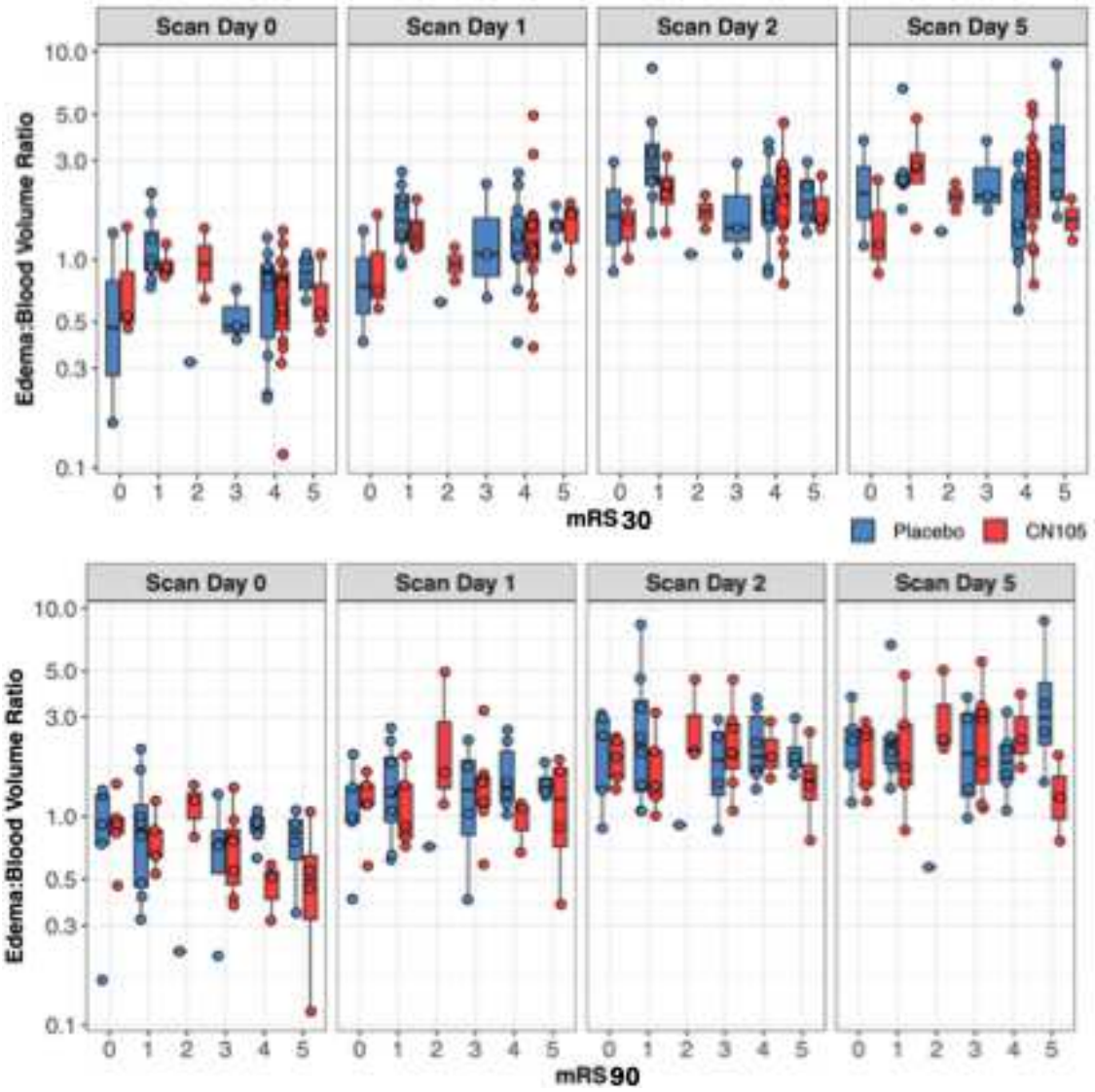


Fig 6. Perihematomal edema by functional outcome and treatment arm across imaging days. The edema:blood volume (E:BV) ratio, used as a hematoma-volume-adjusted measure of perihematomal edema, is shown across serial computed tomography imaging days (Days 0, 1, 2, and 5), stratified by modified Rankin Scale (mRS) score and treatment arm, in participants with acute supratentorial intracerebral hemorrhage enrolled in the S-CATCH trial (n = 56 at day 30 and n = 57 at day 90). Each column corresponds to one scan day; and placebo is shown in blue and CN-105 in red. Results are displayed separately for 30-day mRS (top row) and 90-day mRS (bottom row). E:BV ratio generally increased over time within strata defined by both outcome timepoints. Treatment-group differences were numerically largest among participants with an mRS score of 5; these strata contain few participants, groups differed in the same direction at scan day 0 prior to study drug administration, and no formal subgroup testing was performed..

Table 1. Pre-treatment plasma protein, treatment arm, and their interaction as predictors of perihematomal edema.

Biomarker	CT scan day	R^2	p value
VEGF (ng/L)	Day 0	0.073	0.269
	Day 1	0.176	**0.019**
	Day 2	0.088	0.193
	Day 5	0.031	0.676
TNF-α (ng/L)	Day 0	0.170	**0.022**
	Day 1	0.134	0.061
	Day 2	0.076	0.256
	Day 5	0.107	0.139
S100B (µg/L)	Day 0	0.082	0.221
	Day 1	0.019	0.807
	Day 2	0.014	0.872
	Day 5	0.036	0.622
IL-6 (ng/L)	Day 0	0.055	0.409
	Day 1	0.021	0.776
	Day 2	0.034	0.619
	Day 5	0.041	0.570
D-dimer (mg/L)	Day 0	0.153	**0.036**
	Day 1	0.060	0.367
	Day 2	0.031	0.649
	Day 5	0.028	0.714
CRP (mg/L)	Day 0	0.103	0.132
	Day 1	0.006	0.956
	Day 2	0.014	0.867
	Day 5	0.002	0.995
BNP (ng/L)	Day 0	0.042	0.528
	Day 1	0.012	0.886
	Day 2	0.007	0.943
	Day 5	0.012	0.905

For each computed tomography scan day, a linear model was fitted with log-transformed edema:blood volume (E:BV) ratio as the dependent variable and log-transformed pre-treatment plasma protein concentration, treatment arm, and their interaction as predictors. R^2 is the coefficient of determination for the overall model. P-values test the overall model and do not identify the effects of the individual plasma protein, treatment arm, or interaction term. P-values were not adjusted for multiple comparisons. Models used participants with available imaging and pre-treatment plasma protein measurements. Functional outcome was not included in these models.

Abbreviations: BNP, B-type natriuretic peptide; CRP, C-reactive protein; CT, computed tomography; E:BV, edema:blood volume; IL-6, interleukin-6; S100B, S100 calcium-binding protein B; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor

Statements and Declarations

Funding

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Competing Interests

Daniel T. Laskowitz and Maureen Maughan are affiliated with AegisCN, LLC, which holds licensing rights to CN-105. All other authors declare no competing interests.

Author Contributions

Conceptualization and study design: Daniel T. Laskowitz, Peter G. Kranz, and Michael L. James. Parent trial design and oversight: Tien Meng Cheong, Michael L. James, Nicolas Kon Kam King, Daniel T. Laskowitz, Maureen Maughan, and Vincent Yew Poh Ng. Site principal investigation and clinical oversight: Tien Meng Cheong and Vincent Yew Poh Ng. Trial coordination and regulatory management: Saheen Nehar and Fatimah Misbaah Abdul Rahim. Plasma biomarker analysis and interpretation: Samuel Teshome, Ashley Lin, Liam O'Hara, Daniel T. Laskowitz, Maureen Maughan, and Michael L. James. Imaging analysis and interpretation: Peter G. Kranz, Samuel Teshome, and Michael L. James. Data analysis and statistical interpretation: Samuel Teshome, Liam O'Hara, Ashley Lin, Cina Sasannejad and Michael L. James. Data interpretation: all authors. Manuscript drafting: Samuel Teshome, Ashley Lin, and Michael L. James. All authors critically revised the manuscript for important intellectual content and reviewed and approved the final manuscript.

Ethics Approval

The S-CATCH trial was approved by the SingHealth Centralised Institutional Review Board. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations.

Consent to Participate

Written informed consent was obtained from all participants or their legally authorized representatives.

Data Availability

The data supporting this analysis are available upon request

Code Availability

The analysis code is available upon request

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Reporting checklist

S-CATCH biomarker and imaging secondary analysis

STROBE reporting items

Locations identify sections of the existing manuscript. Additional reported cohort details are stated directly in the response cells. Reference 24 is the published parent-trial report already cited in the manuscript. STROBE covers the biomarker associations; CONSORT covers randomized comparisons. Unavailable information is marked as not reported.

Item	Reporting recommendation	Location and response
1a	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract, Methods; Introduction, final paragraph: randomized parent trial and exploratory secondary analysis identified.
1b	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured Abstract: objectives, design, principal findings, limitations, and conclusions.
2	Explain the scientific background and rationale for the investigation being reported	Introduction: ICH biology, plasma-protein rationale, previous CN-105 studies, and the knowledge gap.
3	State specific objectives, including any prespecified hypotheses	Introduction, final paragraph: post-hoc exploratory associations among plasma proteins, imaging, treatment, and neurological outcome.
4	Present key elements of study design early in the paper	Methods, Study Design and Patient population: secondary analysis of a randomized, double-blind, placebo-controlled phase 2b trial.
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, Study Design and Patient population and Intervention and Outcome Measures: National Neuroscience Institute, Singapore; March 2019–June 2022; plasma days 0–5, CT days 0, 1, 2, and 5, and outcomes at days 30 and 90.
6a	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, Study Design and Patient population: recruitment source, inclusion and exclusion criteria, and consent. Intervention and Outcome Measures: scheduled 30- and 90-day follow-up (±7 days).
6b	(b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable: no matched observational design.
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Intervention and Outcome Measures and Statistical Analysis: nine plasma proteins, mRS, treatment arm, hematoma/PHE volumes, E:BV ratio, model covariates, and interactions.

Item	Reporting recommendation	Location and response
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, Intervention and Outcome Measures: plasma collection, centrifugation and storage; CT acquisition, co-registration and segmentation; and mRS assessment. Assay platform and analytical performance are not reported.

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

STROBE reporting items

Item	Reporting recommendation	Location and response
9	Describe any efforts to address potential sources of bias	Methods: treatment masking through database lock and standardized CT procedures. Discussion, Limitations and Future Directions: small sample, multiplicity, and validation needs. Residual confounding and missing-data bias are not quantified.
10	Explain how the study size was arrived at	Methods, Study Design and Patient population: parent-trial cohort of 60 (30 per arm). The analyses use this existing cohort. A separate biomarker-analysis sample-size calculation is not reported.
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, Statistical Analysis: log-transformed proteins and imaging measures, geometric mean fold changes, ordinal mRS, and mRS 0–2 versus 3–6 and 0–3 versus 4–6. The ambulation rationale is described under Intervention and Outcome Measures.
12a	(a) Describe all statistical methods, including those used to control for confounding	Methods, Statistical Analysis: ordinal and binary regression, mixed-effects models, protein combinations, AICc model selection, ROC analyses, and imaging regression. Biomarker-outcome models are unadjusted; other models state their covariates.
12b	(b) Describe any methods used to examine subgroups and interactions	Methods, Statistical Analysis: protein combinations and protein-by-treatment interactions. Results and Figure 6 describe outcome-defined imaging strata as exploratory.
12c	(c) Explain how missing data were addressed	Methods, Statistical Analysis: three premorbid-mRS exclusions; omission of MMP-3/MMP-9 from initial ordinal models because the first 10 participants could not be included; GFAP exclusion because of many below-quantification values. General imputation and missing-predictor rules are not reported.

Item	Reporting recommendation	Location and response
12d	(d) If applicable, explain how loss to follow-up was addressed	Methods, Intervention and Outcome Measures: 56 available day-30 and 57 day-90 mRS outcomes. Arm counts are CN-105 27/placebo 29 at day 30 and CN-105 27/placebo 30 at day 90. The reason for the unavailable placebo day-30 outcome is not reported.
12e	(e) Describe any sensitivity analyses	No formal sensitivity analysis of the secondary biomarker models is reported. Methods states that the flagged postoperative day-5 scan was retained.

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

STROBE reporting items

Item	Reporting recommendation	Location and response
13a	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods: 60 randomized (30/arm); three excluded from mRS analyses. Available mRS outcomes: day 30, 27 CN-105/29 placebo; day 90, 27/30. The imaging dataset contains 55 participants (27/28), with 52 day-5 scans (26/26). Biomarker-model denominators are not reported.
13b	(b) Give reasons for non-participation at each stage	Methods: premorbid mRS ≥3 explains the three mRS exclusions. The published parent report (reference 24) identifies all three as CN-105 participants with premorbid mRS 4. Other reasons for unavailable secondary outcomes or measurements are not reported.
13c	(c) Consider use of a flow diagram	Participant flow is summarized in items 13a and 13b.
14a	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Parent-cohort characteristics (reference 24, Table 1; CN-105/placebo, n=30 each): age 59.2 (9.6)/58.9 (9.1) years; male 20/22; NIHSS 11.9 (4.7)/12.2 (5.9); hematoma volume 12.8 (11.6)/12.8 (12.1) mL. Continuous values are mean (SD). Subset-specific baseline summaries are not reported.
14b	(b) Indicate number of participants with missing data for each variable of interest	Methods, Statistical Analysis: documented biomarker omissions. One fewer day-30 mRS outcome is available; imaging is available for 55 participants on days 0, 1, and 2 and 52 on day 5. Missing counts for each plasma protein and sampling day are not reported.
14c	(c) Summarise follow-up time (eg, average and total amount)	Methods, Intervention and Outcome Measures: scheduled follow-up at days 30 and 90 (±7 days), with available outcomes in 56 and 57 participants, respectively. Total person-time is not a reported analysis measure.
15	Report numbers of outcome events or summary measures over time	Results and Figures 1–6: biomarker and imaging summaries. In the secondary-analysis outcome summaries, mRS 0–3 occurred in 9/27 CN-105 and 14/29 placebo participants at day 30 and 20/27 and 19/30, respectively, at day 90.

Item	Reporting recommendation	Location and response
16a	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Figures 2, 4 and 5; Table 1: ORs/95% CIs, treatment-associated geometric mean ratios, and overall-model statistics. Methods identifies model covariates; univariate protein-outcome estimates are unadjusted.

STROBE reporting items: S-CATCH biomarker and imaging secondary analysis

Item	Reporting recommendation	Location and response
16b	(b) Report category boundaries when continuous variables were categorized	Methods, Statistical Analysis: mRS 0–2 versus 3–6 and 0–3 versus 4–6; mRS 5 and 6 combined for the Wilcoxon shift analysis.
16c	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Absolute favorable-outcome proportions from the secondary-analysis summaries are given in item 15. No risk-ratio-to-absolute-risk conversion is reported.
17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Methods and Results: exploratory protein combinations, ROC comparisons, treatment interactions, and imaging models. No formal secondary-model sensitivity analysis is reported.
18	Summarise key results with reference to study objectives	Discussion, opening paragraph: findings related to plasma proteins, PHE, treatment, and neurological outcome.
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, Limitations and Future Directions: small sample, limited power, multiplicity, subgroup uncertainty, and need for validation. The direction and magnitude of missing-data and confounding bias are not quantified.
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion and Conclusion: interpretation in relation to prior studies; analyses are hypothesis-generating and did not demonstrate a functional treatment benefit.
21	Discuss the generalisability (external validity) of the study results	Discussion, Limitations and Future Directions: replication and external validation required. Methods identifies a selected, single-site Singaporean trial population.
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Details page and Statements and Declarations: AegisCN, LLC; NIH/NINDS grant 2R42NS108821-02A1 is also listed in the declarations. Author contributions and AegisCN affiliations are disclosed. Sponsor-level roles beyond those author disclosures are not reported.

Guideline: STROBE cohort checklist. https://www.equator-network.org/reporting-guidelines/strobe/

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

CONSORT 2025 reporting items

Applied to the randomized comparisons and relevant parent-trial methods in this secondary report. Parent-trial results are distinguished from secondary-analysis outcome and imaging counts. Official CONSORT 2025 item wording is retained.

Item	Reporting recommendation	Location and response
1a	Identification as a randomised trial	Abstract, Methods: randomized, double-blind, placebo-controlled phase 2b parent trial identified; current report described as an exploratory secondary analysis.
1b	Structured summary of the trial design, methods, results, and conclusions	Structured Abstract: secondary objectives, methods, principal results, unadjusted multiplicity, and cautious conclusions.
2	Name of trial registry, identifying number (with URL) and date of registration	Abstract, Clinical Trial Registration; Details page, Ethical approval: NCT03711903, registered October 16, 2018; registry URL provided.
3	Where the trial protocol and statistical analysis plan can be accessed	Parent publication cited as reference 24. Public access to the full protocol and statistical analysis plan is not specified.
4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	Statements and Declarations, Data Availability and Code Availability: available upon request. Access conditions, data dictionary, and other materials are not specified.
5a	Sources of funding and other support (e.g., supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	Details page and Statements and Declarations: AegisCN, LLC and NIH/NINDS grant 2R42NS108821-02A1. Funder-affiliated authors and contributions are disclosed; additional sponsor-level roles are not reported.
5b	Financial and other conflicts of interest of the manuscript authors	Details page and Statements and Declarations, Competing Interests: AegisCN affiliations and licensing interests, with declarations for other authors.
6	Scientific background and rationale	Introduction: biological rationale and previous CN-105, inflammatory-protein, and imaging evidence.

Item	Reporting recommendation	Location and response
7	Specific objectives related to benefits and harms	Introduction, final paragraph: exploratory biomarker, imaging, and treatment objectives. Primary parent-trial safety findings are reported separately (reference 24).
8	Details of patient or public involvement in the design, conduct and reporting of the trial	Patient and public involvement is not reported.

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

CONSORT 2025 reporting items

Item	Reporting recommendation	Location and response
9	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	Methods, Study Design and Patient population: phase 2b, parallel-group, double-blind, placebo-controlled parent trial; 30 participants per arm. Current analyses are identified as post hoc and exploratory.
10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	Introduction and Statistical Analysis identify post-hoc analyses and the premorbid-mRS exclusions. A complete account of parent-trial protocol amendments is not reported here.
11	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial was conducted	Methods, Study Design and Patient population: National Neuroscience Institute, Singapore; a single recruiting site (reference 24).
12a	Eligibility criteria for participants	Methods, Study Design and Patient population: age, diagnostic imaging, onset window, severity, blood pressure, and exclusion criteria.
12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (e.g., surgeons, physiotherapists)	Additional eligibility criteria for recruiting centers or intervention providers are not reported.
13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	Methods, Intervention and Outcome Measures: CN-105 1.0 mg/kg IV or matching-volume saline, within 12 hours and every 6 hours for 3 days. Reference 24 specifies 30-minute infusions (±10 minutes), a pump and 1.2-μm filter, and a maximum of 13 doses.
14	Pre-specified primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	Methods, Intervention and Outcome Measures and Statistical Analysis: plasma proteins, CT-derived hematoma/PHE measures, mRS assessment times, transformations, and analysis metrics. These are exploratory secondary outcomes.

Item	Reporting recommendation	Location and response
15	How harms were defined and assessed (e.g., systematically, non-systematically)	Parent-trial methods (reference 24): AEs/SAEs and prespecified events monitored throughout follow-up, MedDRA coding, and CTCAE v5.0 grading. Harms are not reanalyzed in this secondary report.
16a	How sample size was determined, including all assumptions supporting the sample size calculation	Methods: parent n=60. Reference 24 reports a safety/feasibility rationale and 80% power for a large day-90 mRS effect (OR 2.5). A separate biomarker-analysis power calculation is not reported.
16b	Explanation of any interim analyses and stopping guidelines	Reference 24: an independent DSMB reviewed interim safety data, including unblinded data, and advised the sponsor on continuation. Formal numerical stopping boundaries are not reported.

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

CONSORT 2025 reporting items

Item	Reporting recommendation	Location and response
17a	Who generated the random allocation sequence and the method used	Reference 24, Randomization and Blinding: block randomization by an independent statistician. Sequence-generation software or algorithm is not specified.
17b	Type of randomisation and details of any restriction (e.g., stratification, blocking and block size)	Reference 24: 1:1 block randomization. Block sizes and stratification restrictions are not specified.
18	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	The allocation-concealment mechanism before assignment is not reported.
19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	Methods and reference 24 describe independent-statistician randomization and blinding of enrollment, treatment, and assessment personnel. Their access to the allocation sequence before assignment is not specified.
20a	Who was blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	Methods, Study Design and Patient population and Intervention and Outcome Measures: participants/representatives, treating teams, and study personnel masked through database lock.
20b	If blinded, how blinding was achieved and description of the similarity of interventions	Methods, Intervention and Outcome Measures: matching-volume normal saline with the same dosing regimen. Additional packaging and appearance procedures are not reported.
21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	Methods, Statistical Analysis: ordinal/binary mRS analyses, protein combinations, longitudinal mixed models, and imaging regression. P-values are not adjusted for multiplicity.
21b	Definition of who is included in each analysis (e.g., all randomised participants), and in which group	Methods: three participants excluded from mRS analyses for premorbid mRS ≥3. Available outcomes: 56 at day 30 and 57 at day 90. These outcome totals are distinct from biomarker-model denominators, which are not reported.

Item	Reporting recommendation	Location and response
21c	How missing data were handled in the analysis	Methods, Statistical Analysis: mRS exclusions, MMP-3/MMP-9 omissions from initial ordinal models, and GFAP quantification limitations. General biomarker missing-data and imputation rules are not reported.
21d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses), distinguishing prespecified from post-hoc	Introduction, Methods, and Results: combinations, ROC comparisons, interactions, and imaging analyses identified as post hoc/exploratory. No formal secondary-model sensitivity analysis is reported.

Reporting checklist continued

S-CATCH biomarker and imaging secondary analysis

CONSORT 2025 reporting items

Item	Reporting recommendation	Location and response
22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	Methods: 30 randomized per arm. Available mRS outcomes: CN-105 27/27 and placebo 29/30 at days 30/90. Reference 24 reports per-protocol counts of 26/28 and >80% treatment compliance in 29 per arm. Outcome, adherence, and model denominators are distinct.
22b	For each group, losses and exclusions after randomisation, together with reasons	Three premorbid-mRS exclusions were in CN-105 (reference 24). One placebo day-30 mRS outcome was unavailable in the secondary summaries. Parent treatment discontinuations: CN-105 1 (urticaria), placebo 3. Other reasons are not reported.
23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	Methods, Study Design and Patient population: March 2019–June 2022 recruitment. Intervention and Outcome Measures: follow-up days 30 and 90 (±7 days). Exact last follow-up date is not reported.
23b	If relevant, why the trial ended or was stopped	The parent trial was completed per protocol (reference 24). The present report is a post-hoc secondary analysis.
24a	Intervention and comparator as they were actually administered (e.g., where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended [fidelity])	Methods describes intended dosing. Reference 24: per-protocol treatment in 26 CN-105/28 placebo participants; >80% compliance in 29 per arm; treatment discontinuations in 1/3.
24b	Concomitant care received during the trial for each group	Methods: standard ICH care and surgery at the blinded treating physician's discretion. Reference 24, Table 4: surgery 0 CN-105/3 placebo; EVD 0/1 and decompression/clot evacuation 0/2.
25	A table showing baseline demographic and clinical characteristics for each group	Reference 24, Table 1: baseline characteristics by randomized arm (30 each). Selected age, sex, NIHSS and hematoma-volume summaries are given in STROBE item 14a above; they describe the full parent cohort.

Item	Reporting recommendation	Location and response
26	For each primary and secondary outcome, by group: the number of participants included in the analysis the number of participants with available data at the outcome time point result for each group, and the estimated effect size and its precision (such as 95% confidence interval) for binary outcomes, presentation of both absolute and relative effect size	Results, Figures 1–6 and Table 1 provide selected estimates, CIs, and model statistics. Available mRS counts are in Methods and item 22a; absolute favorable-outcome counts are in STROBE item 15. Exact biomarker-model denominators are not reported.
27	All harms or unintended events in each group	Parent trial (reference 24, Table 2; CN-105/placebo): any TEAE 27/30 versus 26/30; serious TEAEs 8/30 versus 9/30; pulmonary embolism 2/30 versus 0/30; rash/pruritus 5/30 versus 2/30. No new harms analysis is reported here.
28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post-hoc	Methods and Results: exploratory protein combinations, ROC comparisons, treatment interactions, and imaging models. No formal secondary-model sensitivity analysis is reported.
29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion and Conclusion: exploratory interpretation, comparison with earlier studies, and no established functional benefit. Parent safety findings are reported in reference 24.
30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	Discussion, Limitations and Future Directions: small sample, low power, multiplicity, subgroup uncertainty, and need for validation. Per-model completeness and missing-data bias are not fully characterized.

Guideline: CONSORT 2025 checklist. Hopewell et al. BMJ 2025;389:e081123.
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- SupplementalFigure1.tiff