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Safety and Efficacy of Perispinal Etanercept for Chronic Stroke

A Randomized Clinical Trial

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Abstract

Background and Objectives

Stroke is a leading cause of long-term disability. Etanercept, a competitive tumor necrosis factor-α inhibitor, has been proposed as a potential treatment for post-stroke impairments when given through a perispinal subcutaneous injection. We aimed to evaluate the safety and efficacy of perispinal etanercept in patients with chronic stroke.

Methods

The Perispinal Etanercept for Stroke Outcomes Study was a randomized, double-blind, placebo-controlled, parallel group trial conducted in 3 ambulatory research clinics in Australia and New Zealand. Eligible patients were aged between 18 and 70 years, had a stroke between 1 and 15 years before enrollment, had a modified Rankin Scale score of 2–5, and demonstrated reduced quality of life as assessed by the 36-Item Short Form Survey (SF-36). Patients were randomized in a 1:1 ratio. The primary outcome was the difference in the proportion of participants at day 28 with an improvement of 5 points or more on the SF-36v2 compared with baseline after a single injection of etanercept 25 mg or equivalent placebo. The primary safety outcome was the difference in the proportion over 28 days of serious adverse events after a single injection of etanercept 25 mg or equivalent placebo. The primary outcome and safety were analyzed in the intention-to-treat population. Participants were followed up 56 days after the first injection of perispinal etanercept.

Results

Recruitment ceased early because of lack of continued funding. We screened 147 participants, of whom 126 were enrolled and randomized (63 etanercept: 63 placebo; 48 [38%] female, median (interquartile range) age 54.5 (45.0–60.0) years, median time since stroke 3 years). The primary outcome of improvement occurred in 33 of 63 participants (53%) in the etanercept arm and 36 of 63 participants (58%) in the placebo arm (adjusted odds ratio 0.82, 95% CI 0.40–1.67, standardized risk difference −5%, 95% CI −22% to 13%). The proportion of serious adverse events was similar in both treatment arms.

Discussion

Perispinal etanercept was safe, but we found no evidence of improvement in quality of life and other efficacy outcomes compared with placebo.

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Supplementary Material

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Glossary

DSMB = Data Safety Monitoring Board; **ITT** = intention-to-treat; **MoCA** = Montreal Cognitive Assessment; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **PESTO** = Perispinal Etanercept for Stroke Outcomes Study; **SF-36** = 36-Item Short Form Survey; **TNF** = tumor necrosis factor; **VAS** = Visual Analog Scale.

Trial Registration Information

The trial was registered at anzctr.org.au (ACTRN12620001011976) on October 7, 2020. Patients were enrolled between November 4, 2020, and September 1, 2023.

Classification of Evidence

This study provides Class I evidence that in patients with imaging-confirmed ischemic or hemorrhagic stroke, perispinal etanercept (25 mg) injection does not improve the patients' quality of life 28 days after injection.

Introduction

Stroke is a leading cause of long-term disability.[1] Despite advances in management, a considerable proportion of stroke survivors are left with disabling neurologic impairments. Medical treatment options are limited.

Tumor necrosis factor-α (TNF-α) has been implicated in the pathophysiology of stroke recovery.[2-4] TNF-α is a proinflammatory cytokine that plays a critical role in the neuroinflammatory response after stroke. Elevated levels of TNF-α have been associated with blood-brain barrier disruption, neuronal injury, and impaired neuroplasticity, suggesting that modulation of TNF-α activity may support functional recovery.[2,3] Preclinical studies have demonstrated that inhibiting TNF-α signaling can reduce secondary brain injury and improve outcomes in experimental models.[3] Emerging hypotheses further propose that persistent microglial activation, sustained through an autocrine positive feedback loop involving TNF-α, may underlie chronic neurologic dysfunction after stroke.[5] However, although biologically plausible, this model remains speculative and requires further experimental validation.

Etanercept competitively inhibits TNF-α but is unable to cross the blood-brain barrier because of its high molecular weight.[6] Nevertheless, etanercept has been proposed to improve post-stroke impairments when administered subcutaneously in the interspinous cervical spine, followed by head-down positioning.[7-9] This method purportedly bypasses the blood-brain barrier. In a preclinical study, CNS penetration with perispinal administration of radiolabeled etanercept was shown in a single rat.[10] However, a subsequent study challenged this assertion, finding no evidence for the passage of radiolabeled etanercept into the CNS after perispinal injection in rats.[11] Instead, the drug was observed to accumulate locally in the perispinal region. Nevertheless, human observational studies have documented substantial improvements in various post-stroke impairments. A retrospective review of 617 patients with chronic stroke—treated an average of 3.5 years after stroke with some treated even decades later—reported significant improvements in motor function, spasticity, sensory perception, cognition, and pain relief after perispinal etanercept treatment.[7] Effects persisted at least for weeks after a single administration, with some patients reporting additional effects with repeated administration.[7] An additional report in 3 patients showed improvements within minutes in multiple domains after a single administration, with further improvement after a second administration.[12] A pilot, double-blind placebo controlled randomized trial of 26 patients with chronic post-stroke pain tested 2 doses of perispinal etanercept. This study was stopped after an interim analysis showed a significant, rapid improvement in pain levels and improvement in mobility of the shoulder. There was no improvement in fatigue and depression levels or sit-to-stand measures.[8]

Interviews with patients who received off-label etanercept in private clinics further indicated that treatment is offered to patients with moderate-to-severe disability and that receiving 2 injections is common practice.

To generate high-quality evidence, stroke survivors in Australia successfully lobbied the Australian government to fund a clinical trial to independently evaluate the current practice of etanercept to treat stroke.

The aim of the Perispinal Etanercept for Stroke Outcomes Study (PESTO) trial was to assess whether perispinal administration of etanercept (25 mg) was superior to placebo in improving health-related quality of life in patients with imaging-confirmed ischemic or hemorrhagic stroke with chronic disability and reduced quality of life 28 days after injection.

Methods

Study Design and Participants

The PESTO trial was a phase 2b, double-blind, placebo-controlled, randomized study conducted across 3 outpatient

centers in Australia and New Zealand. The study adopted a parallel group design with concealed allocation, blinded assessment of outcomes, and analysis based on the intention-to-treat (ITT) principle. An independent Data Safety Monitoring Board (DSMB) oversaw the trial safety and reviewed study conduct. The investigator team included a stroke survivor, who provided essential guidance on selecting outcome measures, structuring study visits to minimize participant burden, and shaping the patient-facing materials from a lived-experience perspective. The study was conducted following the principles of Good Clinical Practice.

Standard Protocol Approvals, Registrations, and Patient Consents

Study protocols and amendments were approved by the ethics committee at each site. All participants or their legal representatives provided written informed consent. The first and most recent version of the signed protocol and the statistical analysis plan finalized before the study data lock are provided as supplemental material (eSAP1). The trial was registered at the Australian and New Zealand Clinical Trial Registry (ACTRN12620001011976), and the trial protocol was published.[13] The following amendments to the inclusion criteria were made during the course of the trial to increase recruitment rates: Age at time of stroke was expanded and permitted inclusion of patients with stroke at age 16 or 17 but were at least 18 at time of inclusion (protocol version 2.1) and inclusion of patients with stroke up to age 70 (previously 65, protocol version 2.0). Time since stroke was increased to 15 years (previously 5 years, protocol version 2.0). We also permitted inclusion of patients with modified Rankin Scale (mRS) score 2 with reduced quality of life, as measured using a 36-Item Short Form Survey (SF-36) score of <80 (previously only mRS scores 3–5 were included, protocol version 2.1).

Participant Criteria

The study included adults aged 18–70 years who had an imaging-confirmed ischemic or hemorrhagic stroke 1–15 years before enrollment. We enriched the trial population by including participants with moderate-to-severe disability, as indicated by a mRS score of 3–5 and an SF-36 score of 95 or less, or a mRS score of 2 with an SF-36 score less than 80.[14] Exclusion criteria were contraindications to etanercept, certain infectious diseases, immunosuppressive agent use, severe heart conditions, malignancy history, or recent botulinum toxin injection as listed in the detailed criteria in the protocol.

Randomization and Allocation

Randomization was stratified by whether the prerandomization quality-of-life questionnaire was completed by the participant, or, if not possible, by a proxy; baseline mRS scores (dichotomized as mRS scores 2–3 vs mRS scores 4–5); and time since stroke (1–5 years vs >5 years after stroke onset). Stratification by baseline mRS scores was performed using combined categories (mRS scores 2–3 vs mRS scores 4–5), rather than individual mRS scores. Participants were first randomized in a 1:1 ratio to receive either a single dose of the etanercept (etanercept arm) or placebo (the control arm) using a centralized computer-generated random assignment procedure with permuted blocks of various sizes as part of the Research Electronic Data Capture electronic case record form. At the second step of the randomization procedure conducted at the same time point, the participants in the placebo arm were subsequently randomized into receiving either the second dose of placebo or a single dose of etanercept at day 28 after the first injection (based on a 2:1 allocation ratio), whereas participants in the etanercept arm were subsequently randomized into receiving either a single dose of placebo or the second dose of etanercept at day 28 (based on a 1:2 allocation ratio). This resulted in 3 equally sized, covariate-balanced arms (placebo n = 56, single dose of etanercept n = 56, and two doses of etanercept n = 56) for the secondary dose-response analysis of the efficacy outcome at day 56. The study flow is presented in Figure 1. A researcher not otherwise involved in the trial undertook the randomization and allocation to treatment arms, thereby ensuring allocation concealment. The treatment allocation was sent electronically to the unblinded study pharmacist who prepared the investigational product. Because etanercept may produce a yellow discoloration, the syringe was wrapped in a yellow transparent foil by the unblinded pharmacist and handed over to the blinded study investigator before the delivery. Participants, study investigators, study site personnel assessing outcomes, and the sponsor were masked to treatment group allocation.

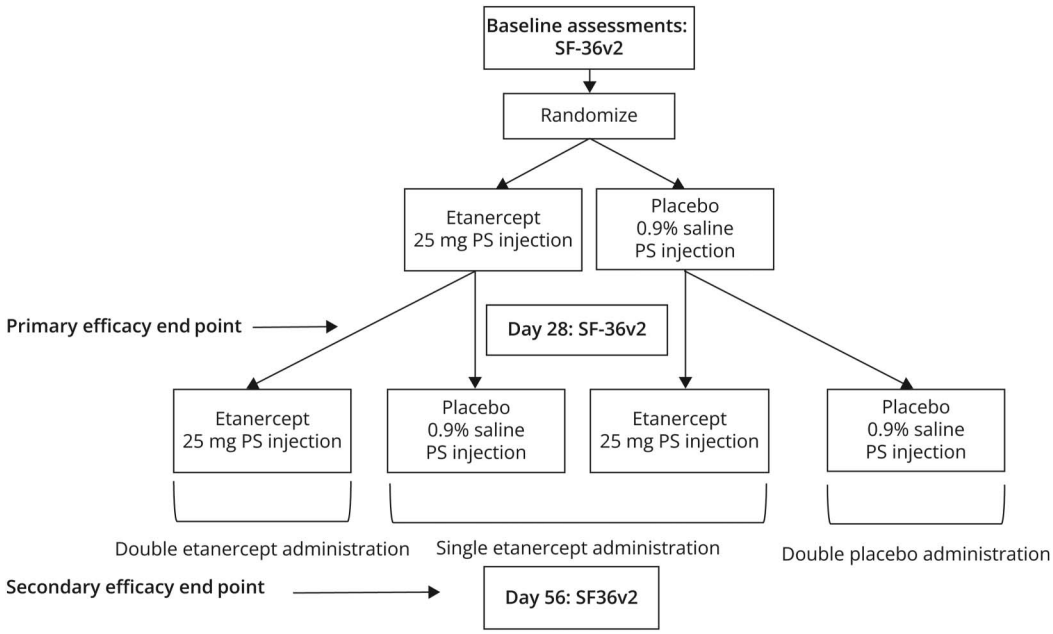
Study Procedures

After screening for eligibility, participants underwent a blood test to screen for hepatitis B, hepatitis C, and tuberculosis. Women of childbearing age underwent pregnancy testing. Two weeks after screening, rating scale assessments were performed after which patients received investigational product. A single dose of etanercept (25 mg) or placebo was administered subcutaneously by an investigator in the posterior cervical region at C6-C7 or C7-T1. Administration of etanercept was harmonized across recruiting sites, and investigators were trained to give etanercept according to published methods.[15] After administration, participants were positioned in a Trendelenburg position for 4 minutes and were observed for adverse reactions for another 30 minutes. After 28 days, rating scale assessments were performed and a second dose of etanercept or placebo was administered. After another 28 days, rating scale assessments were performed.

Outcome Measures

The primary efficacy end point was the proportion of participants with at least a 5-point improvement in the SF-36v2 score at 28 days after the first intraperitoneal injection.[16] This was defined as either a 5-point improvement in the Physical Component Summary score, or in the Mental Component Summary score, or a 5-point improvement in the sum of the

Figure 1 Study Timeline



SF-36 = 36-Item Short Form Survey.

change in the Physical Component Summary score or the Mental Component Summary score of the SF-36v2 between baseline and day 28. This approach was chosen to capture treatment effects that may manifest differently across functional and mental health domains. The SF-36v2 was selected as the primary outcome measure because of its comprehensive assessment of health-related quality of life across multiple domains, accommodating the heterogeneous impairments present in stroke survivors. Consultation with a stroke survivor on the investigator team emphasized the importance of evaluating overall well-being, rather than domain-specific functional gains, supporting the selection of the SF-36v2. In selecting a 5-point threshold for our dichotomous classification, we aimed to balance the need for a clear, clinically interpretable benchmark with the desire to capture potentially smaller but meaningful changes in a chronic stroke population. Although typical minimally important differences for SF-36v2 often hover around 10 points, we opted for a more sensitive cutoff to avoid missing subtle improvements in this population.

The SF-36v2 is a validated, 36-question patient-reported outcome measure, assessing 8 domains (physical function, bodily pain, vitality, role limitations due to emotional health or physical health, general health, social function, and mental health).[17] Scores are scaled between 0 and 100, and higher scores are indicative of a better quality of life. The SF-36v2 was scored using proprietary software supplied under license from Qualitymetric[18] to calculate the Total, the Physical, and the Mental Component subscores of the SF-36v2.[16] The secondary efficacy end point was the difference in the proportion of participants at day 56 who showed an improvement of at least 5 points or more on the SF-36v2 compared with baseline across the 3 treatment arms (placebo, single administration of etanercept, 2 administrations of etanercept). For the primary outcome analysis at day 28, participants were classified based on the treatment received within the first 28-day period. Those who received their first dose of etanercept only in the second 28-day period were categorized as placebo recipients for the primary end point.

The primary safety outcome was serious adverse events occurring up to 28 days after treatment. The secondary safety outcome was serious adverse events occurring up to 56 days after the first injection across the 3 treatment groups (placebo, single dose of etanercept, and two doses of etanercept).

Exploratory End Points

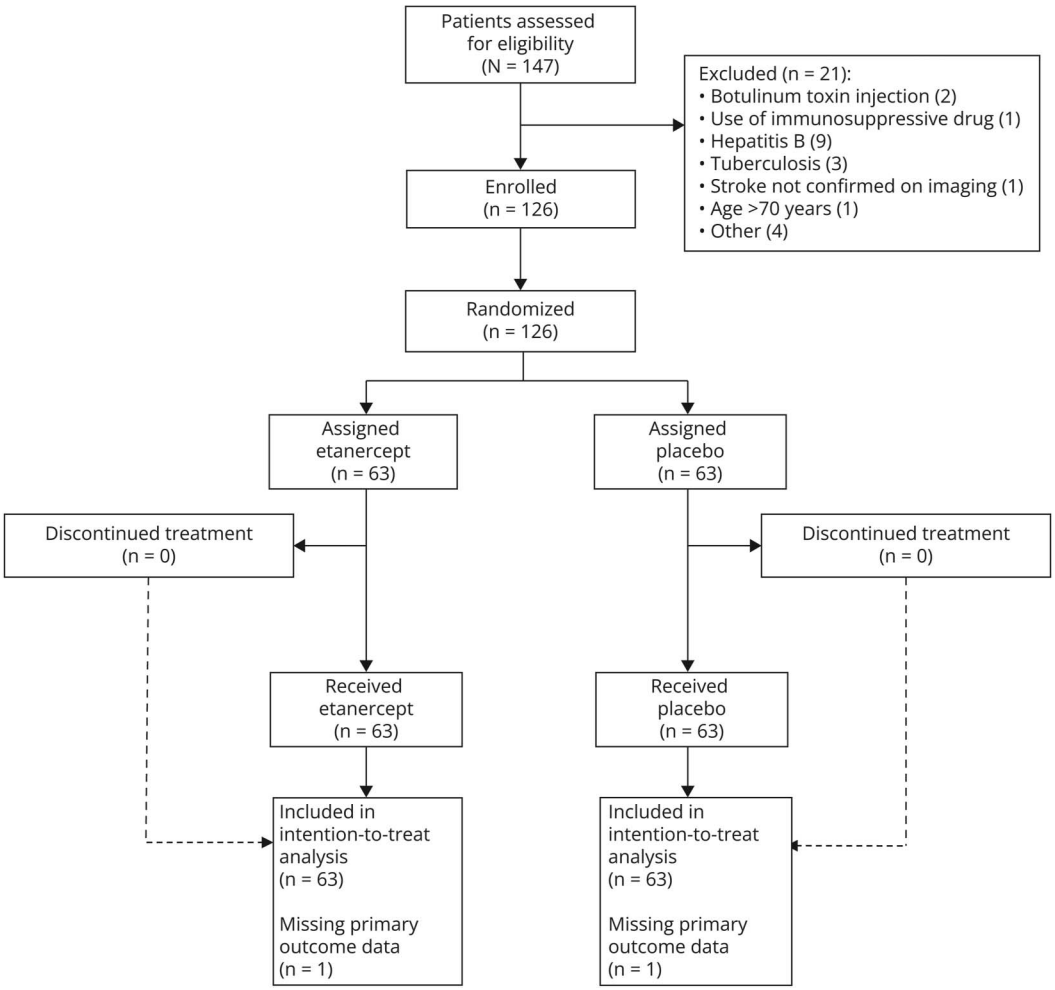
The exploratory end points aimed to provide a broad assessment of etanercept's impact on various aspects of stroke recovery, including neurologic function (NIH Stroke Scale [NIHSS]), independence (Functional Independence Measure), global disability (mRS), fatigue (Fatigue Assessment Scale), anxiety (General Anxiety Disorder-7), depression (Patient Health Questionnaire-9), cognitive ability (Montreal Cognitive Assessment [MoCA]), and pain measured with a 100-point Visual Analog Scale (VAS).

Statistical Considerations

Sample Size

Based on unpublished data from a previous placebo-controlled study in stroke survivors, we assumed that the SF-36v2 score

Figure 2 Study Disposition



would improve by at least 5 points in approximately 11% of participants in the placebo group.[19] We conservatively estimated the rate of improvement in the etanercept group to be 30% based on a very high rate of improvement (85% or more) in neurologic functioning reported in the observational studies with etanercept.[7] This led to a planned total sample size of 160 (equally distributed between 2 arms), with a 2-sided α of 0.05 to yield a power of 0.80. To allow for potential dropouts, we increased this sample size to 168.

Outcome Analysis

The analysis for the primary outcome and all secondary efficacy and safety outcome analyses were conducted on an ITT basis. In addition to the ITT analysis, an "as-treated" analysis was also conducted. In the presence of missing data for the SF-36v2 outcome, sensitivity analyses were conducted under a range of assumptions about the missing data. The sensitivity of the results to plausible departures from missing at random was explored as part of an ITT analysis strategy using pattern mixture modeling.[20] We report the prespecified pattern mixture analysis to ensure transparency and maintain consistency with our statistical analysis plan.

For the primary and secondary efficacy outcome, binary logistic regression was used, with treatment arm(s) as the independent variable, the improvement of 5 points or more on the SF-36v2 at day 28 (or day 56) compared with baseline as the dependent variable, and baseline SF-36v2 score and time since stroke in years as treatment covariates for adjustment purposes. The treatment effect is presented as adjusted odds ratio and standardized risk difference with the corresponding 95% CIs.[21] For the primary and secondary safety hypothesis, the Firth logistic regression model was used, with treatment arm(s) as the independent variable and the presence or absence of SAEs over 28 days (or 56 days) as the dependent variable.

For exploratory analyses, differences in mRS outcomes at 28 days and at 56 days after first injection between the treatment groups were investigated using generalized odds ratios stratified by baseline mRS score with tied observations split equally between the arms.[22,23]

Differences in all other exploratory outcomes at 28 days and 56 days after first injection between the placebo arm and the

Table 1 Baseline Characteristics of the ITT Population (n = 126)

	Total (n = 126)	Placebo (n = 63)	Etanercept (n = 63)
Demographics and risk factors			
Age at enrollment, y, median (IQR)	54.50 (45.00–60.00)	55.00 (46.00–60.00)	54.00 (45.00–61.00)
Age at time of last stroke, y, median (IQR)	49.50 (41.00–57.00)	49.00 (42.00–57.00)	50.00 (39.00–58.00)
No. of years from last stroke, y, median (IQR)	3.00 (1.00–5.00)	3.00 (2.00–4.00)	2.00 (1.00–5.00)
Stroke type, n (%)			
Ischemic stroke	85 (67)	38 (60)	47 (75)
Intracerebral hemorrhage	39 (31)	24 (38)	15 (24)
Subarachnoid hemorrhage	2 (2)	1 (2)	1 (2)
Unknown	0 (0)	0 (0)	0 (0)
Sex, female, n (%)	48 (38)	25 (40)	23 (37)
Hypertension, n (%)	N = 123 55 (45)	27 (43)	N = 60 28 (47)
Hypercholesterolemia, n (%)	N = 123 43 (35)	N = 62 15 (24)	N = 61 28 (46)
Atrial fibrillation, n (%)	N = 124 15 (12)	6 (10)	N = 61 9 (15)
Diabetes, n (%)	N = 122	N = 62	N = 60
IDDM	3 (2)	2 (3)	1 (2)
NIDDM	19 (16)	6 (10)	13 (22)
Current smoker, n (%)	N = 122 14 (11)	8 (13)	N = 59 6 (10)
Past smoker (ceased within past 2 y combined with ceased more than 2 y ago), n (%)	N = 111 53 (48)	N = 55 28 (51)	N = 56 25 (45)
Coronary artery disease, n (%)	N = 124 8 (6)	3 (5)	N = 61 5 (8)
Assessments			
Baseline NIHSS score, median (IQR)	5.50 (3.00–9.00)	6.00 (3.00–9.00)	5.00 (3.00–8.00)
mRS score at baseline, n (%)			
2	12 (10)	5 (8)	7 (11)
3	62 (49)	30 (48)	32 (51)
4	44 (35)	25 (40)	19 (30)
5	8 (6)	3 (5)	5 (8)
SF-36 at screening measured by participant, total score, median (IQR)	N = 94 40.00 (31.04–50.57)	N = 46 41.25 (28.91–51.04)	N = 48 38.88 (31.95–49.43)
SF-36 at screening measured by proxy, total score, median (IQR)	N = 32 40.31 (25.52–50.52)	N = 17 43.28 (30.78–44.53)	N = 15 39.53 (21.72–56.41)
SF-36v2 at baseline (proxy and participant, total score), median (IQR)	N = 125 79.34 (69.63–88.58)	N = 63 78.69 (69.89–88.86)	N = 62 79.51 (68.30–88.58)
SF-36v2 at baseline by participant, PCS, median (IQR)	N = 96 38.40 (32.51–44.10)	N = 47 38.66 (32.21–43.20)	N = 49 36.85 (32.72–44.62)
SF-36v2 at baseline by participant, MCS, median (IQR)	N = 96 39.86 (33.68–48.97)	N = 47 39.97 (32.66–49.94)	N = 49 39.76 (34.61–46.64)
SF-36v2 at baseline by proxy, PCS, median (IQR)	N = 29 33.62 (28.01–39.37)	N = 16 35.22 (30.73–40.56)	N = 13 32.18 (26.13–36.92)

Continued

Table 1 Baseline Characteristics of the ITT Population (n = 126) *(continued)*

	Total (n = 126)	Placebo (n = 63)	Etanercept (n = 63)
SF-36v2 at baseline by proxy, MCS, median (IQR)	N = 29 44.10 (37.12–54.90)	N = 16 45.82 (33.80–56.67)	N = 13 43.93 (38.30–51.36)
PHQ-9 total score, median (IQR)	8.00 (5.00–12.00)	8.00 (4.00–15.00)	7.00 (5.00–12.00)
FAS total score, median (IQR)	27.00 (22.00–33.00)	27.00 (22.00–33.00)	28.00 (22.00–33.00)
GAD-7 score, median (IQR)	N = 125 5.00 (2.00–9.00)	N = 62 5.50 (2.00–10.00)	5.00 (3.00–8.00)
VAS score, median (IQR)	N = 124 15.50 (0.50–60.00)	N = 62 13.00 (2.00–50.00)	N = 62 28.50 (0.00–65.00)
MoCA score, median (IQR)	N = 105 25.00 (22.00–27.00)	N = 55 25.00 (22.00–27.00)	N = 50 25.00 (22.00–27.00)
FIM, median (IQR)	N = 125 113.00 (101.00–120.00)	N = 62 112.00 (97.00–121.00)	115.00 (103.00–120.00)

Abbreviations: FAS = Fatigue Assessment Scale; FIM = Functional Independence Measure; GAD-7 = General Anxiety Disorder-7; IDDM = insulin-dependent diabetes mellitus; IQR = interquartile range; ITT = intention-to-treat; MCS = Mental Component Summary; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NIDDM = non–insulin-dependent diabetes mellitus; NIHSS = NIH Stroke Scale; PCS = Physical Component Summary; PHQ-9 = Patient Health Questionnaire-9; SF-36 = 36-Item Short Form Survey; VAS = Visual Analog Scale.

etanercept arm were investigated using quantile regression, with the respective outcome measure at 28 days (or 56 days) as the dependent variable, treatment arm as the independent variable, and baseline value of the outcome variable and time since stroke in years as adjustment covariates. The models were run for the 25th, 50th (median), and 75th percentile of the outcome distributions. Given the exploratory nature of these analyses and the use of percentile regression at key distribution quantiles (25th, 50th, and 75th percentiles), results should be interpreted for the purposes of estimating the effect magnitude and uncertainty, rather than for hypothesis testing. No formal adjustments were undertaken to constrain the overall type I error associated with the secondary, tertiary, and exploratory analyses.

Subgroups

The following subgroups were prespecified: age at time of stroke (young: 16–45 years vs older >45 years), sex, number of years since stroke (1–5 years inclusive vs >5 years), stroke type (ischemic stroke vs other), baseline mRS score (mild to moderate [2–3] vs severe [4–5]), SF-36v2 completed by the participant vs proxy, hypertension (present vs absent), diabetes (type 1 and type 2 vs no diabetic history), and atrial fibrillation (present vs absent).

Analyses were conducted using Stata 18.0 Standard Edition and R 4.2.3 statistical software.

Data Availability

Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, can be made available to others on reasonable request and after signing appropriate data sharing agreements. Data access requests should be sent to vincent.thijs@florey.edu.au. Data requests must be approved by all the respective ethics boards and appropriate data custodians.

Results

Recruitment ceased early because of lack of continued funding. We screened 147 participants and enrolled and randomized 126 participants between November 4, 2020, and September 1, 2023. Sixty-three participants were randomized to the etanercept group and 63 to the placebo group for evaluation of the primary outcome at day 28 (ITT population, trial profile in Figure 2).

Of 63 participants randomized to the placebo arm for the first injection, 21 participants were randomized to etanercept at the second injection and 42 to 2 placebo injections. Of 63 participants randomized to the etanercept arm for the first injection, 20 participants were randomized to placebo at the second and 43 to 2 etanercept injections.

Overall, this resulted in 42 participants randomized to 2 placebo injections, 41 participants to a single injection of etanercept (either at the first or second injection), and 43 participants to 2 etanercept injections for the secondary efficacy outcome at day 56 (study disposition, Figure 1).

The median age at time of stroke was 49.5 years (interquartile range [IQR] 45–60), with 48 women (38%). The baseline demographics and clinical characteristics for the primary efficacy analysis are given in Table 1 and for the secondary efficacy analysis in Table 2 (eTables 1 and 2 for the as-treated analyses). Minor numerical imbalances were noted between treatment groups in the baseline mRS strata (placebo: 56% mRS scores 2–3, 44% mRS scores 4–5; etanercept: 62% mRS scores 2–3, 38% mRS scores 4–5). A higher proportion of participants in the etanercept group had an ischemic stroke compared with the placebo group (75% vs 60%, respectively). The median NIHSS score was 5.5, and there were 52 (41%)

Table 2 Baseline Characteristics for the Secondary Efficacy Outcome (ITT Population, n = 126)

	Placebo (n = 42)	Single dose of etanercept (n = 41)	Two doses of etanercept (n = 43)
Demographics and risk factors			
Age at enrollment, y, median (IQR)	54.50 (45.00–61.00)	55.00 (48.00–60.00)	53.00 (43.00–61.00)
Age at time of last stroke, y, median (IQR)	48.50 (41.00–58.00)	51.00 (44.00–56.00)	49.00 (38.00–56.00)
No. of years from last stroke, y, median (IQR)	3.00 (2.00–5.00)	2.00 (1.00–4.00)	3.00 (1.00–5.00)
Stroke type, n (%)			
Ischemic stroke	26 (62)	24 (59)	35 (81)
Intracerebral hemorrhage	15 (36)	17 (41)	7 (16)
Subarachnoid hemorrhage	1 (2)	0 (0)	1 (2)
Subtype unknown	0 (0)	0 (0)	0 (0.00)
Sex, female, n (%)	17 (40)	19 (46)	12 (28)
Hypertension, n (%)	18 (43)	19 (46)	N = 40 18 (45)
Hypercholesterolemia, n (%)	N = 41 9 (22)	17 (41)	N = 41 17 (41)
Atrial fibrillation, n (%)	5 (12)	2 (5)	N = 41 8 (20)
Diabetes, n (%)	N = 41		N = 40
IDDM	2 (5)	0 (0)	1 (3)
NIDDM	4 (10)	7 (17)	8 (20)
Current smoker, n (%)	5 (12)	N = 40 6 (15)	N = 40 3 (8)
Past smoker (ceased within past 2 y combined with ceased more than 2 y ago), n (%)	N = 36 16 (44)	N = 37 21 (57)	N = 38 16 (42)
Coronary artery disease, n (%)	2 (5)	2 (5)	N = 41 4 (10)
Assessments			
Baseline NIHSS score, median (IQR)	6.00 (3.00–9.00)	5.00 (2.00–8.00)	5.00 (3.00–8.00)
mRS score at baseline, n (%)			
2	3 (7)	4 (10)	5 (12)
3	20 (48)	20 (49)	22 (51)
4	17 (40)	14 (34)	13 (30)
5	2 (5)	3 (7)	3 (7)
SF-36 at screening measured by participant, total score, median (IQR)	N = 31 41.56 (28.91–49.48)	N = 30 38.57 (31.56–55.05)	N = 33 41.09 (32.97–48.28)
SF-36 at screening measured by proxy, total score, median (IQR)	N = 11 43.28 (28.13–44.53)	N = 11 34.38 (23.12–48.85)	N = 10 40.31 (19.69–56.41)
SF-36v2 at baseline (proxy and participant, total score), median (IQR)	N = 42 79.10 (70.25–89.92)	N = 40 77.79 (68.59–88.44)	N = 43 80.13 (68.30–89.55)
SF-36v2 at baseline by participant, PCS, median (IQR)	N = 32 39.80 (32.53–43.98)	N = 30 37.26 (31.92–40.88)	N = 34 37.79 (32.72–49.17)
SF-36v2 at baseline by participant, MCS, median (IQR)	N = 32 41.18 (32.99–50.03)	N = 30 39.16 (33.67–54.94)	N = 34 39.41 (35.24–45.27)
SF-36v2 at baseline by proxy, PCS, median (IQR)	N = 10 34.47 (26.48–39.58)	N = 10 34.20 (26.13–42.22)	N = 9 32.53 (31.79–36.92)

Continued

Table 2 Baseline Characteristics for the Secondary Efficacy Outcome (ITT Population, n = 126) *(continued)*

	Placebo (n = 42)	Single dose of etanercept (n = 41)	Two doses of etanercept (n = 43)
SF-36v2 at baseline by proxy, MCS, median (IQR)	N = 10 45.82 (33.36,59.57)	N = 10 43.40 (37.12–53.34)	N = 9 47.82 (37.78–52.66)
PHQ-9 total score, median (IQR)	7.00 (4.00–16.00)	8.00 (5.00–11.00)	7.00 (5.00–12.00)
FAS total score, median (IQR)	26.00 (22.00–33.00)	28.00 (22.00–33.00)	27.00 (21.00–33.00)
GAD-7 score, median (IQR)	N = 41 6.00 (3.00, 11.00)	5.00 (2.00–9.00)	5.00 (2.00–8.00)
VAS score, median (IQR)	17.50 (4.00–51.00)	N = 39 26.00 (3.00–68.00)	10.00 (0.00–59.00)
MoCA score, median (IQR)	N = 36 25.50 (23.00–27.00)	N = 35 25.00 (22.00–27.00)	N = 34 24.00 (22.00–27.00)
FIM, median (IQR)	113.50 (99.00–121.00)	N = 40 111.50 (97.00–119.50)	115.00 (104.00–120.00)

Abbreviations: FAS = Fatigue Assessment Scale; FIM = Functional Independence Measure; GAD-7 = General Anxiety Disorder-7; IDDM = insulin-dependent diabetes mellitus; IQR = interquartile range; ITT = intention-to-treat; MCS = Mental Component Summary; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NIDDM = non–insulin-dependent diabetes mellitus; NIHSS = NIH Stroke Scale; PCS = Physical Component Summary; PHQ-9 = Patient Health Questionnaire-9; SF-36 = 36-Item Short Form Survey; VAS = Visual Analog Scale.

with a baseline mRS score of 4 or 5. The Total SF-36v2 score at baseline was 79 (IQR 70–89), Physical Component Score 37 (IQR 32–42), and Mental Component Score 40 (IQR 34–50).

We included 126 participants in the evaluation of the primary efficacy outcome and 126 in the evaluation of the secondary outcome (Figure 1 and eFigure 1).

The primary outcome and exploratory outcomes at day 28 are provided in Table 3 for the ITT population and eTable 3 for the as-treated population.

On the prespecified ITT analysis, there were 33 participants (53%) allocated to etanercept and 36 participants (58%) allocated to placebo with improvement by 5 or more points on the SF-36v2 (complete case, adjusted odds ratio 0.82, 95% CI 0.40–1.67, standardized risk difference −5%, 95% CI −22% to 13%). The individual median changes for the 3 SF-36 subscales (Total, Physical, and Mental Component summaries) are summarized in Table 3, indicating no differences between etanercept and placebo.

The secondary efficacy outcome and exploratory outcomes at 56 days are given in Table 4 for the ITT analysis and in eTable 4 for the as-treated analysis. In the prespecified ITT analysis (complete case), the proportion of participants who showed improvement by at least 5 or more points on the SF-36v2 on day 56 was similar among patients receiving etanercept twice (n = 22/41, 54%), a single dose of etanercept (n = 25/38, 66%), or placebo twice (n = 21/36, 58%).

There were 2 serious adverse events (SAEs) between recruitment and day 28 (1 participant had a seizure on the day of placebo injection, and 1 participant received a diagnosis of renal carcinoma with pancreatic and brain metastasis on day 15, assigned etanercept) and 3 additional SAEs between day 28 and day 56 (1 participant, assigned a second dose of placebo on day 28, had a second seizure; 1 participant, assigned double placebo, had a neck of femur fracture on day 54; and 1, assigned etanercept initially and placebo on day 28, had malaise and possible aspiration on day 53).

No differences were found in exploratory outcomes at day 28 and at day 56, except for the VAS score for pain at day 56. Median regression indicated a difference of −9.5 (95% CI −17.30 to −1.7) for the single dose vs placebo and −9.5 for the double dose vs placebo (95% CI −18.47 to −0.53). Regression at the 75th percentile showed a difference for the single dose vs placebo (−10.43, 95% CI −19.63 to −1.24). The values for the 25th percentile were similar (Table 4 and eTable 4 for the as-treated analysis).

Subgroups for the primary outcome are shown in Figure 3. There were no treatment-by-subgroup interactions, and no differences were observed in any subgroup.

Classification of Evidence

This study provides Class I evidence that in patients with imaging-confirmed ischemic or hemorrhagic stroke, perispinal etanercept (25 mg) injection does not improve the patients' quality of life 28 days after injection.

Discussion

This randomized controlled trial evaluated the effect of perispinal etanercept on quality of life in individuals with chronic

Table 3 Primary and Exploratory Outcomes at Day 28 (ITT Population)

	Placebo (n = 63)	Etanercept (n = 63)	Effect size (95% CI)
Primary efficacy outcome (n = 126)			
Participants at day 28 with an improvement of 5 points or more on the SF-36v2 compared with baseline, change in Mental or Physical or Total SF-36v2 score	36 (58) n = 62	33 (53) n = 62	aOR: 0.82 (0.40 to 1.67)[a] to $p = 0.585$ Standardized risk difference: −0.05 (−0.22 to 0.13)
SF-36v2 Total change, median (IQR)	4.01 (0 to 8.41)	3.46 (−0.53 to 9.99)	NA
SF-36v2 Physical change, median (IQR)	1.46 (−1.57 to 4.13)	1.74 (−0.80 to 4.9)	NA
SF-36v2 Mental change, median (IQR)	2.89 (0 to 7.12)	1.51 (−1.9 to 7.55)	NA
Primary safety outcome (n = 126)			
Participants with serious adverse events over 28 d	There are no sufficient data (2 cases, 1 in each group)		aOR: NA Standardized risk difference: NA
Exploratory outcomes (n = 126)			
NIHSS score at 28 d, median (IQR)	5 (2 to 8) n = 62	4 (2 to 8) n = 62	Q1: 0.00 (−1.26 to 1.26) Median: 0.03 (−0.39 to 0.46) Q3: 0.00 (−0.51 to 0.51)
FIM, median (IQR)	112.5 (98.5 to 121) n = 60	114 (100.5 to 121) n = 60	Q1: 0.0 (not defined) Median: 0 (0 to 0) Q3: 0.08 (−0.91 to 1.07)
mRS score, stratified by baseline mRS score, not adjusted for years since onset, median (IQR)	3 (3 to 4) n = 62	3 (3 to 4) n = 62	Pooled OR: 0.89 (0.72 to 1.11)
FAS score, median (IQR)	25 (21 to 29) n = 62	26 (20 to 32) n = 61	Q1: −0.48 (−3.33 to 2.37) Median: −0.27 (−3.24 to 2.7) Q3: 0.69 (−1.63 to 3.02)
GAD-7 score, median (IQR)	3 (1 to 6) n = 61	3.5 (1 to 7) n = 62	Q1: 0.5 (−0.69 to 1.69) Median: 0.00 (−1.26 to 1.26) Q3: 0.67 (−0.64 to 1.99)
PHQ-9 score, median (IQR)	7 (4.5 to 11) n = 60	7 (3 to 11.5) n = 60	Q1: −0.79 (−2.50 to 0.93) Median: 0.75 (−0.95 to 2.44) Q3: 1.28 (−0.38 to 2.93)
VAS score for pain, median (IQR)	19 (2 to 45) n = 61	17 (0 to 57) n = 61	Q1: 0.0 (−6.72 to 6.72) Median: 0.06 (−3.91 to 4.03) Q3: −2.39 (−9.7 to 4.9)
MoCA score, median (IQR)	26 (23 to 28) n = 54	26 (24 to 28) n = 51	Q1: 0.34 (−1.02 to 1.7) Median: 0.2 (−0.87 to 1.27) Q3: 0.61 (−0.34 to 1.56)

Abbreviations: aOR = adjusted odds ratio; FAS = Fatigue Assessment Scale; FIM = Functional Independence Measure; GAD-7 = General Anxiety Disorder-7; IQR = interquartile range; ITT = intention-to-treat; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PHQ-9 = Patient Health Questionnaire-9; Q1 = 25th percentile; Q3 = 75th percentile; SF-36 = 36-Item Short Form Survey; VAS = Visual Analog Scale.
Data are n (%), n/N (%), or median (IQR).
[a]Pattern mixture model sensitivity analysis: aOR 0.83 (0.40–1.69), $p = 0.599$.

post-stroke disability. Although the study did not reach its planned enrollment target, the observed results suggest that any potential benefit of etanercept on the primary outcome is likely to be modest. The difference between groups in the proportion of participants achieving a ≥5-point increase in the SF-36v2 score was small, and the CIs were wide, encompassing both possible benefit and no effect. These findings indicate that perispinal etanercept, when administered according to the protocol used in this trial, is unlikely to produce large improvements in quality of life in this population. The trial was not powered to reliably detect small treatment effects, and the early termination further limits the precision of estimates. Secondary outcomes, including dose-response relationships and changes in pain scores, should be interpreted cautiously, given the exploratory nature of these analyses.

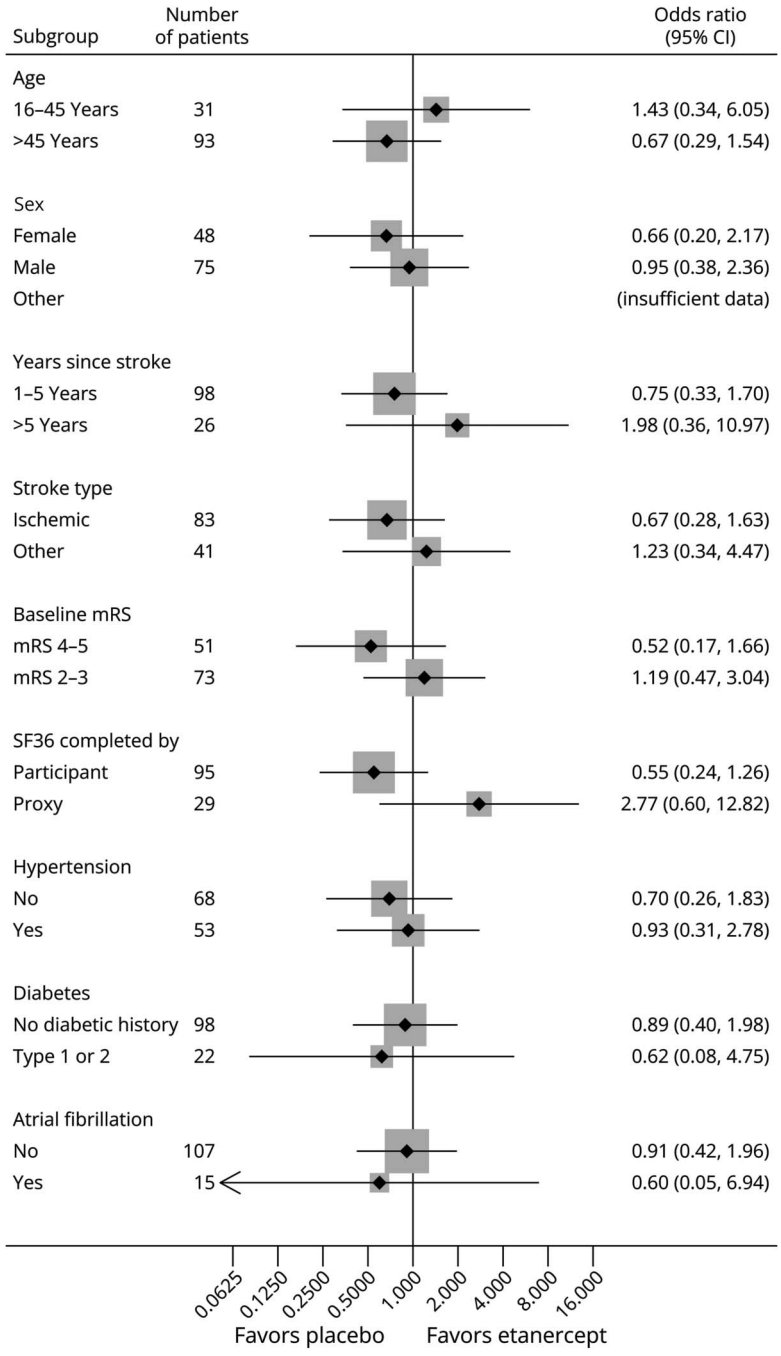
We deliberately included patients with a variety of impairments after stroke, rather than a more homogeneous group with only a single impairment. A seminal article on perispinal etanercept found significant improvements in multiple impairments after stroke, including motor, sensory, cognitive, psychological, and behavioral function; aphasia and pain; and pseudobulbar affect, as well as spasticity and urinary incontinence.[7] Our trial also reflects current practice to

Table 4 Secondary and Exploratory Outcomes at Day 56 (ITT)

	Placebo (n = 42)	Single dose of etanercept (n = 41)	Two doses of etanercept (n = 43)	Effect size, single dose vs placebo (95% CI)	Effect size, 2 doses vs placebo (95% CI)
Secondary efficacy outcome (intention-to-treat population; n = 126)					
Participants at day 56 with an improvement of 5 points or more on the SF-36v2 compared with baseline, change in Mental or Physical or Total SF-36v2 score	21 (58) n = 36	25 (66) n = 38	22 (54) n = 41	aOR: 1.42 (0.55 to 3.68)[a] Standardized risk difference: 0.08 (−0.14 to 0.3)	aOR: 0.86 (0.34 to 2.13)[b] Standardized risk difference: −0.04 (−0.26 to 0.18)
SF-36v2 Total change, median (IQR)	2.94 (−3.89 to 9.25)	5.74 (0.5 to 15.8)	1.16 (−4.38 to 10.17)		
SF-36v2 Physical change, median (IQR)	2.43 (−0.83 to 4.39)	3.64 (0 to 6.01)	1.86 (−1.27 to 3.48)		
SF-36v2 Mental change, median (IQR)	2.53 (−4.43 to 6.57)	4.3 (−0.66 to 10.02)	0.95 (−4.08 to 8.88)		
Secondary safety outcome (intention-to-treat population; n = 126)					
Participants with serious adverse events over 56 d	1 (2)	2 (5)	1 (2)	aOR: NA Standardized risk difference: NA	aOR: NA Standardized risk difference: NA
Exploratory outcomes					
NIHSS score, median (IQR)	6 (3 to 9) n = 39	5 (2 to 7) n = 39	4 (2 to 7) n = 42	Q1: 0.0 (−1.19 to 1.19) Median: −0.02 (−0.72 to 0.68) Q3: 0.0 (−0.73 to 0.73)	Q1: 0.06 (−1.00 to 1.13) Median: −0.02 (−0.70 to 0.65) Q3: 0.0 (−0.67 to 0.67)
FIM, median (IQR)	114 (102 to 121) n = 39	110 (97 to 121) n = 37	115.5 (101 to 121) n = 42	Q1: 0.0 (−1.30 to 1.30) Median: 0.0 (−0.81 to 0.81) Q3: 0.4 (−1.84 to 2.65)	Q1: 0.0 (−1.21 to 1.21) Median: 0.0 (−0.76 to 0.76) Q3: −0.3 (−1.93 to 1.31)
mRS, median (IQR), not adjusted for years, scores 4 and 5 combined	3 (3 to 4) n = 39	3 (3 to 4) n = 39	3 (3 to 4) n = 42	GPCT OR: 0.95 (0.77 to 1.11) to $p = 0.609$	
FAS score, median (IQR)	28 (18 to 32) n = 35	24 (20 to 32) n = 37	26 (21 to 30) n = 41	Q1: −0.12 (−4.46 to 4.22) Median: 0.29 (−2.73 to 3.30) Q3: −0.4 (−3.71 to 2.91)	Q1: −0.50 (−3.41 to 2.40) Median: −0.86 (−3.65 to 1.94) Q3: −0.15 (−4.04 to 3.74)
GAD-7 score, median (IQR)	5 (0 to 11) n = 35	3 (0 to 8) n = 37	4 (1 to 7) n = 41	Q1: −0.15 (−1.66 to 1.35) Median: −0.67 (−2.64 to 1.31) Q3: 0.0 (−2.80 to 2.80)	Q1: 0.31 (−1.30 to 1.91) Median: 0.0 (−1.99 to 1.99) Q3: 1 (−0.82 to 2.82)
PHQ-9 score, median (IQR)	5.5 (3 to 11) n = 34	6 (2 to 9.5) n = 36	5 (3 to 12) n = 41	Q1: −1.26 (−4.30 to 1.77) Median: 0.53 (−2.26 to 3.32) Q3: 1.09 (−1.95 to 4.14)	Q1: −0.04 (−2.26 to 2.17) Median: −0.02 (−2.42 to 2.37) Q3: 1 (−2.07 to 4.07)
VAS score for pain, median (IQR)	22 (9 to 53) n = 35	10 (0 to 52) n = 37	9 (0 to 45) n = 41	Q1: −1.73 (−10.52 to 7.06) Median: −9.5 (−17.30 to −1.7) Q3: −10.43 (−19.63 to −1.24)	Q1: −2.05 (−10.89 to 6.78) Median: −9.5 (−18.47 to −0.53) Q3: −3.96 (−15.92 to 8.00)
MoCA score, median (IQR)	26 (24 to 29) n = 30	27 (22 to 28) n = 30	27 (25 to 29) n = 31	Q1: 0.33 (−1.16 to 1.82) Median: 0.11 (−1.51 to 1.73) Q3: −0.1 (−1.39 to 1.19)	Q1: 0.48 (−0.90 to 1.86) Median: 0.33 (−1.13 to 1.79) Q3: 0.3 (−1.02 to 1.62)

Abbreviations: aOR = adjusted odds ratio; FAS = Fatigue Assessment Scale; FIM = Functional Independence Measure; GAD-7 = General Anxiety Disorder-7; IQR = interquartile range; ITT = intention-to-treat; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PHQ-9 = Patient Health Questionnaire-9; Q1 = 25th percentile; Q3 = 75th percentile; SF-36 = 36-Item Short Form Survey; VAS = Visual Analog Scale.
Data are n (%), n/N (%), or median (IQR).
[a] Pattern mixture model sensitivity analysis: aOR 1.64 (0.67–3.99).
[b] Pattern mixture model sensitivity analysis: aOR 1.08 (0.45–2.58).

Figure 3 Prespecified Subgroup Analysis



administer perispinal etanercept in patients with a variety of impairments, rather than isolated pain or motor impairment only. The quality-of-life outcome was similarly chosen to identify potential benefits of perispinal etanercept with high sensitivity in a variety of domains after stroke.

Although the study did not demonstrate a statistically significant treatment effect, the findings are nonetheless important for informing clinical practice. Given previous claims of substantial benefit with perispinal etanercept, our results suggest that such claims may not be supported by high-quality clinical trial data. While the lack of a significant treatment effect may reduce enthusiasm for this intervention, the study contributes valuable evidence to the field, reinforcing the need for robust, controlled evaluations of novel therapies.

Our study does not support the previously stated effect of etanercept. One might question the justification for conducting a trial like PESTO, given the limited preclinical and clinical data available.[7,8,12,24] Perispinal etanercept was not developed following a rigorous clinical development plan for regulatory approval. Nevertheless, the stroke survivor

community, along with the professional stroke community, felt that a rigorous trial testing current clinical application was needed to confirm its efficacy and safety.[25] Randomized trials initiated because of consumer advocacy have previously been successful in discontinuing unproven practices.[26,27]

Our study has limitations. We did not pair the intervention with standardized rehabilitation.[28] This was considered; however, our goal was to test current practice, and no standardized rehabilitation is offered with off-label perispinal etanercept. Participants continued with their habitual rehabilitation programs if they were already engaged in them. However, we did not systematically assess or control for variations in rehabilitation activities. The planned sample size was not achieved because the trial stopped early. The decision to stop was, however, not based on interim analysis for efficacy or futility but due to lower than desired recruitment during the coronavirus disease 2019 pandemic. Yet, this may have biased the results. Nevertheless, the treatment estimates make a large treatment effect unlikely using the confidence distribution effects framework.[29] Differences in recovery trajectories between ischemic and hemorrhagic stroke could have influenced outcomes. Given that patients were enrolled between 1 and 15 years after stroke, the well-described early (<1 year) post-stroke differences in recovery are less likely to have played a role; however, long-term differences in recovery patterns could still have affected results. In addition, our study's underrepresentation of women may limit the generalizability of these findings, especially given the higher prevalence of inflammatory disorders in women and the potential for sex-specific treatment responses. The staggered enrollment over a long recruitment period may also have introduced bias; however, we believe that this risk is minimal, given the lack of major changes in standard care or available treatments of chronic stroke during that time frame. While the observed placebo response rate was substantially higher than initially estimated, the study findings remain valid, as CIs provide a more informative measure of the precision of the treatment effect than retrospective concerns about power calculations. The trial results suggest that etanercept did not produce a clinically meaningful benefit compared with placebo, despite the higher-than-expected response rate in the control group.

Quality-of-life outcomes are not commonly used as a primary end point in stroke clinical trials, where more traditional measures are recommended.[30] Our secondary outcomes, which included non–proxy-based outcome measures, such as the NIHSS, mRS, and MoCA, also did not indicate a difference between etanercept and placebo. Theoretically, including a third group of patients assigned to a nonplacebo control would have allowed for causal inference of a placebo effect.[31] While minor imbalances in baseline characteristics were observed, such as baseline mRS grouping, these were consistent with chance variation and expected in trials using block randomization, particularly when recruitment ceases early. They are not expected to have influenced the primary outcome. In a minority of cases, proxy responders were used for the SF-36v2, which may have introduced bias because proxies can systematically overestimate or underestimate quality-of-life domains compared with patient self-report.[32,33] However, this was used as a stratification variable in randomization, and we did not observe an interaction in subgroup analysis. Other non–proxy-based outcome scales also did not show differences. We also did not incorporate relevant peripheral inflammatory markers to more fully delineate any systemic immunologic effects or potential safety concerns. Although long-term safety data for etanercept exist in chronic inflammatory conditions, its prolonged use in stroke survivors remains unclear; our short trial duration prevents definitive conclusions.

In summary, although this phase 2b, placebo-controlled trial demonstrated that etanercept is safe, it did not show an improvement in quality of life.

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Author Contributions

V.N. Thijs: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G.C. Cloud: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. N. Gilchrist: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. B. Parsons: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. F. Tilvawala: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.K. Ho: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Ruthnam: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Stanislaus: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. N. Sprigg: drafting/revision of the manuscript for content, including medical writing for content;

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Disclosure

V.N. Thijs reports speaker fees for Amgen, Allergan, Astra Zeneca, Atricure, BMS, Bayer, Boehringer Ingelheim, and Medtronic, unrelated to this publication; is on the editorial board for *Annals of Neurology*, *Neurology®*, *International Journal of Stroke*, and the *European Stroke Journal*; is on the steering committee of the Librexia trial, for which he receives modest compensation from Janssen; and chairs the DSMB of the Evaluating the Safety and Efficacy of Telemedicine Neurology Assessments on a Mobile Stroke Unit and the Emview Study. G.C. Cloud reports honoraria for speaking engagements and participation in advisory board consultation for Astra Zeneca. P.M. Bath is Stroke Association Professor of Stroke Medicine and an emeritus NIHR Senior Investigator; and has consulted for and received honoraria from CoMind, DiaMedica, Phagenesis, and Roche. J. Bernhardt is supported by the NHMRC Australia; has received honoraria for presentations to the American Congress of Rehabilitation Medicine, Moleac P/L, and the University Hospital of Bern; has received travel support from the World Stroke Organization, the Swiss Congress CHUV, the Global Stroke Alliance, and the Dutch Society of Neurorehabilitation; is an associate editor for the *International Journal of Stroke* and Section Editor, *Stroke Recovery and Rehabilitation for Stroke*; is the executive chair of the International Stroke Recovery and Rehabilitation Alliance; is a member on the Scientific Advisory of academic institutions in Norway and India; is the chair of the data safety monitoring board for the iWHO, SCI-MT, and ESTRELL trials; and is on the steering committee of the PISCES, UPLIFT, and ENABLE trials. All other authors report no disclosures. Go to Neurology.org/N for full disclosures.

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