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Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion–diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study

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WH, AJF, AD, MK, RK, LJL, HAR, PAT, KWO, and SW were members of the steering committee. WH, AJF, YA, AD, FG, MK, SP, DS, LHS, MS, PAR, and SW participated in the design and conduct of the study. All authors participated in the analysis or interpretation of the data, and in the writing and reviewing of the manuscript.

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Conflicts of interest

WH was a consultant and advisory board member for Paion and has received honoraria for being the chairman of the steering committee from Forest, Paion, and Lundbeck. AJF has been a consultant for Forest and Paion, and a North American principal investigator for the DEDAS and DIAS-2 studies. YA was an employee of Paion Deutschland GmbH at the time of and analysis of the study. AD received fees as a consultant, paid speaker, or advisory board member from Ferrer Grupo, Paion, Lundbeck, Boehringer Ingelheim, Pfizer, and BMS. JBF has served as a consultant and received honoraria and lecture fees from Forest and Paion. MK has received honoraria for attending the DIAS-2 steering committee meetings from Forest. LJL is an employee of Forest Laboratories. SP has served as a consultant to Paion and a member of the DIAS-2 imaging committee. PAR has received speaker fees from and consulted for Paion. HAR has been a consultant for Forest and Paion, and has received fees as consultant for research agreements with GE Healthcare, Bracco, BTG, and Nuvelo. LHS has served as a consultant for Coaxia, the Research Triangle Institute, and the Massachusetts Department of Public Health, and has occasionally served as an expert reviewer of malpractice cases related to cerebrovascular disease. MS is an employee of Paion Deutschland GmbH, a member of the management board of Paion AG, and a shareholder in the company. PAT has received an honorarium for services on the DIAS-2 steering committee. KWO is an employee of Paion Deutschland GmbH and owns stock options in Paion. MW receives funding from the National Center for Research Resources, Grant KL2 RR024130, GE Healthcare, Philips Medical Systems, and Boston Scientific, and was a consultant for Paion, Lundbeck, and Concentric at the time of the study. FG, DS, JSL, and SW have no conflicts of interests.

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Summary

Background—Previous studies have suggested that desmoteplase, a novel plasminogen activator, has clinical benefit when given 3–9 h after the onset of the symptoms of stroke in patients with presumptive tissue at risk that is identified by magnetic resonance perfusion imaging (PI) and diffusion-weighted imaging (DWI).

Methods—In this randomised, placebo-controlled, double-blind, dose-ranging study, patients with acute ischaemic stroke and tissue at risk seen on either MRI or CT imaging were randomly assigned (1:1:1) to 90 μg/kg desmoteplase, 125 μg/kg desmoteplase, or placebo within 3–9 h after the onset of symptoms of stroke. The primary endpoint was clinical response rates at day 90, defined as a composite of improvement in National Institutes of Health stroke scale (NIHSS) score of 8 points or more or an NIHSS score of 1 point or less, a modified Rankin scale score of 0–2 points, and a Barthel index of 75–100. Secondary endpoints included change in lesion volume between baseline and day 30, rates of symptomatic intracranial haemorrhage, and mortality rates. Analysis was by intention to treat. This study registered with ClinicalTrials.gov, NCT00111852.

Findings—Between June, 2005, and March, 2007, 193 patients were randomised, and 186 patients received treatment: 57 received 90 μg/kg desmoteplase; 66 received 125 μg/kg desmoteplase; and 63 received placebo. 158 patients completed the study. The median baseline NIHSS score was 9 (IQR 6–14) points, and 30% (53 of 179) of the patients had a visible occlusion of a vessel at presentation. The core lesion and the mismatch volumes were small (median volumes were 10·6 cm^3 and 52·5 cm^3, respectively). The clinical response rates at day 90 were 47% (27 of 57) for 90 μg/kg desmoteplase, 36% (24 of 66) for 125 μg/kg desmoteplase, and 46% (29 of 63) for placebo. The median changes in lesion volume were: 90 μg/kg desmoteplase 14·0% (0·5 cm^3); 125 μg/kg desmoteplase 10·8% (0·3 cm^3 placebo −10·0% (−0·9 cm^3). The rates of symptomatic intracranial haemorrhage were 3·5% (2 of 57) for 90 μg/kg desmoteplase, 4·5% (3 of 66) for 125 μg/kg desmoteplase, and 0% for placebo. The overall mortality rate was 11% (5% [3 of 57] for 90 μg/kg desmoteplase; 21% [14 of 66] for 125 μg/kg desmoteplase; and 6% [4 of 63] for placebo).

Interpretation—The DIAS-2 study did not show a benefit of desmoteplase given 3–9 h after the onset of stroke. The high response rate in the placebo group could be explained by the mild strokes recorded (low baseline NIHSS scores, small core lesions, and small mismatch volumes that were associated with no vessel occlusions), which possibly reduced the potential to detect any effect of desmoteplase.

Introduction

Thrombolytic therapy with intravenous alteplase is the only approved treatment for acute ischaemic stroke, but its use is currently restricted to within 3 h after the onset of symptoms.[1] The results of a meta-analysis suggested that the treatment window for intravenous alteplase might be extended up to 4·5 h.[2] This result was confirmed by ECASS III (the European

Cooperative Acute Stroke Study), which showed a statistically significant improved outcome for patients who were treated with alteplase within 3 to 4·5 h after the onset of symptoms of stroke.[3]

In the past decade, the identification of ischaemic brain tissue at risk of infarction (which corresponds to the penumbra region identified experimentally) by magnetic resonance perfusion–diffusion weighted imaging MR PI–DWI) mismatch has been a focus of investigation.[4] Prospective cohort studies and the DEFUSE (Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution) and EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) randomised studies have provided evidence for the clinical usefulness of the MR PI–DWI mismatch.[5,6] Perfusion CT is an alternative imaging modality to identify ischaemic brain tissue at risk. Published data have suggested that perfusion CT might be comparable to MRI, despite the known limitations of CT with regard to brain coverage.[7–9]

Desmoteplase, a highly fibrin-specific plasminogen activator, is in development for thrombolysis after the 3 h time window.[10,11] High fibrin specificity, no activation by β amyloid,[12,13] and the absence of neurotoxicity[14] make desmoteplase a promising thrombolytic drug. In the DIAS (Desmoteplase In Acute ischemic Stroke) and DEDAS (Dose Escalation study of Desmoteplase in Acute ischemic Stroke) phase II studies, doses of 90 μg/kg and 125 μg/kg desmoteplase had acceptable safety profiles, led to superior reperfusion compared with placebo, and apparent clinical efficacy up to 9 h after the onset of symptoms in patients who were selected by PI–DWI mismatch on MRI.[10,11] DIAS-2, a phase III study, was done to confirm the results of the DIAS/DEDAS studies and to investigate further the clinical efficacy and safety of desmoteplase in patients with acute ischaemic stroke who have tissue at risk, as assessed by MR PI–DWI or perfusion CT.

Methods

Patients

Patients aged between 18 and 85 years, who had a National Institutes of Health stroke scale (NIHSS) score between 4 and 24 points, clinical signs of cerebral hemispheric infarction, and onset of symptoms within 3–9 h, were included. In addition, potentially salvageable tissue at risk—the presumptive penumbra—estimated as at least 20% of the tissue with perfusion disturbance compared with the core of acute ischaemic injury was required. Patients were excluded if they were at increased risk of bleeding or if they had contraindications to the imaging modalities. Panel 1 lists the inclusion and exclusion criteria. The duration of participation in the study was 90 days. An independent data monitoring committee monitored the risk–benefit profile during the study. All other study personnel and patients were blinded to treatment assignment for the period of the study. A central imaging reading group assessed the clinical and imaging data independently and in a blinded fashion. The steering committee comprised experts in stroke and cardiovascular disease and two representatives from the sponsors of the study.

The protocol and all amendments were approved by the institutional review board and regulatory authority at each centre. Written informed consent was obtained from all patients or from their legal representatives, as appropriate.

Procedures

Sites were designated as MR or CT on the basis of preference and experience. A few sites were dual-certified to use a second imaging technique in case of contraindications to the first technique (eg, metal implants, claustrophobia, or known intolerance to contrast dye). CT or

MRI was done at baseline to assess vessel status, core lesion volume, perfusion deficits, and to exclude intracranial bleeding. Mismatches were evaluated qualitatively at each site, in accordance with local practice, as a visually apparent mismatch of core and perfusion lesions. Vessel patency, as assessed with the adapted thrombolysis in myocardial infarction (TIMI) criteria,[15] and quantitative mismatch assessments were done retrospectively by the central imaging reading group. To assess the change in infarct volume from baseline, CT or MRI was done at day 30. Sites were required to use the same modality at baseline and at day 30. A safety CT was done in all patients 24–72 h after treatment and before antithrombotic therapy was started, to document any intracranial bleeding. The need for additional imaging was established by clinical status. Panel 2 shows the imaging assessment schedule.

Treatment was allocated on a 1:1:1 ratio by computer-generated randomisation codes, which were stratified by centre and communicated by an interactive voice response system to the investigator's site. A designated independent person at the participating centres reported baseline data (age, weight, time since onset of symptoms, and imaging modality) and was informed about the amount of study medication to be prepared. After preparation and blinding of the volume with a label, the syringe was handed to the investigator for administration to the patient.

Patients received either of the bodyweight-adjusted doses (90 μg/kg or 125 μg/kg) of desmoteplase or placebo as one intravenous bolus over 1–2 min. Placebo and desmoteplase were prepared and given in an identical manner. The maximum dose given corresponded to 100 kg bodyweight.

The primary efficacy endpoint was good clinical outcome at day 90, which required fulfilment of all three of the following criteria: improvement in NIHSS of 8 points or more from baseline (or NIHSS ≤1 point); modified Rankin scale (mRS) score of 0–2 points; and Barthel index (BI) of 75–100. Secondary endpoints were change in infarct volume between baseline and day 30 and the clinical response on the individual components of the primary endpoint at day 90.

The primary safety outcomes were the rate of symptomatic intracranial haemorrhage, defined as intracranial haemorrhage confirmed by appropriate diagnostic imaging that led to an increase of 4 points or more in NIHSS score at 72 h, and mortality at 90 days. Causes of death were also assessed.

This trial is registered with ClinicalTrials.gov, number NCT00111852.

Statistics

For the sample size estimates, a superiority of desmoteplase over placebo of 45% versus 20% was assumed. The placebo response rate was based on the combined experience of the investigators in the DIAS/DEDAS studies, which used similar inclusion criteria (except for CT-based inclusion) and the same primary efficacy parameter. The absolute difference between desmoteplase and placebo (25%) was chosen to preserve about half of the absolute difference seen in the combined DIAS/DEDAS results for the patients in the 125 μg/kg desmoteplase group. This difference is contained within the 95% CI for the absolute difference between 125 μg/kg desmoteplase and placebo. On the basis of a power of 80% to detect a significant difference (two-sided p=0·05), 62 patients were to be enrolled in each of the three groups.

Efficacy analysis was based on the intention-to-treat population. The last observation carried forward (LOCF) method was used to impute missing values; only post-baseline values were used for imputation. Patients who died were assigned the worst possible score on each scale for all subsequent visits. All statistical tests were two-sided hypothesis tests done at the 5% level of significance; CIs were two-sided with a 95% confidence level throughout. To control

for the overall type I error for multiple comparisons with placebo, an overall global statistical test was done first. Comparisons between each of the desmoteplase groups and placebo were to be done only if the overall treatment test was statistically significant at the 5% level. The primary efficacy parameter was analysed with a logistic regression model, with treatment group, geographical region, baseline NIHSS score, and age as explanatory variables. The homogeneity of treatment effects for the primary efficacy parameter between CT and MRI was assessed with the same logistic regression model as that used for the primary efficacy analysis but with the addition of modality and treatment group by modality interaction as explanatory variables. Subgroup analyses by time from stroke onset to treatment and by sex were also done.

Safety analyses were done on the intention-to-treat population with descriptive statistics. Bleeding events were categorised as either symptomatic or asymptomatic intracranial haemorrhages (ie, any intracranial haemorrhage that did not fulfil the criteria of symptomatic intracranial haemorrhage), major haemorrhagic event (anaemia or episode of bleeding other than intracranial haemorrhage that was deemed to be life threatening by the investigator or was associated with a decrease in haemoglobin concentration of 40 g/L or more or required two units or more of blood cells to be transfused), and minor haemorrhagic events. Bleeding events were summarised by treatment group. All-cause mortality per group was also recorded.

The overall DIAS-2 population was compared with the pooled DIAS and DEDAS populations with respect to baseline characteristics: Fisher's exact test was used for binary variables and the Wilcoxon–Mann–Whitney test was used for all other variables.

Selected baseline characteristics that potentially predicted a clinical response (age, NIHSS score, mismatch volume, core lesion volume, and vessel occlusion) were compared within and between the MRI and CT subgroups. Within subgroups, continuous variables were analysed with a two-way ANOVA, with treatment group and geographical region as factors, and with the Cochran–Mantel–Haenszel test controlled for region for binary outcomes. Comparisons between subgroups were done with Fisher's exact test on the binary variables and the Wilcoxon–Mann–Whitney test on all other variables. Prespecified, blinded imaging analyses included the rate of symptomatic intracranial haemorrhage, abnormalities of volume of diffusion (MRI-selected patients only), and abnormalities of cerebral blood volume (CT-selected patients only). Other imaging analyses included the presence or absence of vessel occlusion (TIMI score of 0–1 points, assessed by MR angiography or CT angiography), and absolute and relative mismatch volumes. In addition, the central reading of the imaging studies was compared with the local reading. Clinical response rates in the subgroup of patients with (TIMI 0–1 points) or without (TIMI 2–3 points) proximal vessel occlusion were also analysed, retrospectively.

***Panel* 1: Main selection criteria**

Inclusion criteria

- Informed consent
- Age 18–85 years
- Treatment within 3–9 h of the onset of stroke symptoms
- Score of 4–24 points on the National Institutes of Health stroke scale (NIHSS) with clinical signs of hemispheric infarction (eg, hemiparesis) that are suggestive of ischaemic stroke
- A distinct penumbra (at least 20%), measured by magnetic resonance perfusion imaging (PI) and diffusion-weighted imaging (DWI) or perfusion CT, in the

territory of the middle cerebral artery, anterior cerebral artery, or posterior cerebral artery with a hemispheric distribution

Exclusion criteria

- Patients not able to receive study medication within 60 min of completing diagnostic imaging screening
- Rapidly improving neurological symptoms such that the rate of improvement is projected to give the patient an NIHSS score of <4 at randomisation
- Prestroke modified Rankin scale (mRS) score of more than 1 point (indicating previous disability)
- Consciousness level greater than 2 points on question 1a of NIHSS
- History or clinical presentation of intracranial haemorrhage, subarachnoid haemorrhage, arteriovenous malformation, aneurysm, or cerebral neoplasm
- Suspected acute occlusion of the vertebral or basilar artery
- Current use of oral anticoagulants and a prolonged prothrombin time (international normalised ratio >1·6)
- Use of heparin, except for low-dose subcutaneous heparin, in the previous 48 h and a prolonged partial thromboplastin time that exceeded the upper limit of the normal range of the local laboratory
- Use of inhibitors of glycoprotein IIb–IIIa within the past 72 h; use of single oral inhibitor of platelets (clopidogrel or low-dose aspirin) before entry into the study was permitted
- Baseline blood glucose concentration less than 50 mg/dL or greater than 300 mg/dL; patients with blood glucose concentrations between 200–300 mg/dL could be included only if the blood glucose concentration decreased to less than 200 mg/dL after treatment with antidiabetic drugs and before the study medication was given
- Uncontrolled hypertension, defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg on at least two separate occasions at least 10 min apart, or blood pressure that required aggressive treatment to reduce it to within these limits
- Hereditary or acquired haemorrhagic diathesis
- Another stroke or a serious head injury within the previous 6 weeks
- A history of stroke in a patient with diabetes, unless blood glucose concentration was within the range indicated above
- Exposure to thrombolytic drugs within the previous 72 h
- Core of infarct involved more than a third of the middle cerebral artery territory or all of the anterior cerebral artery territory
- Evidence of intracerebral haemorrhage or subarachnoid haemorrhage (regardless of age), arteriovenous malformation, cerebral aneurysm, or cerebral neoplasm seen on imaging (incidental meningioma and microbleeds per se were not exclusion criteria)
- Well-developed parenchymal hyperintensity seen on fluid attenuated inversion recovery (FLAIR), T2*-weighted, or echoplanar imaging T2-weighted images, or

pronounced hypodensity on CT, which indicates a subacute infarction or enhancement with morphologic features that suggest the lesion is older than 9 h

- Occlusion of the internal carotid artery on the side of the lesion
- Any contraindication to the imaging techniques

***Panel* 2: Imaging assessment schedule**

Baseline

MRI

DWI, T2*, MRA, PI, T2–FLAIR

CT

Non-contrast CT, perfusion CT, CT angiography

24–72 h

MRI

Non-contrast CT

CT

Non-contrast CT

Day 30

MRI

DWI, T2–FLAIR

CT

Non-contrast CT

DWI=diffusion-weighted imaging. T2*=T2*-weighted imaging. MRA=magnetic resonance angiography. PI=perfusion imaging. T2–FLAIR=T2-weighted fluid attenuated inversion recovery imaging.

Role of the funding source

The sponsors were involved in the design of the study, the collection, analysis, and interpretation of the data, and in writing the study report. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between June, 2005, and March, 2007, 186 patients from 52 hospitals in 12 countries in Europe, Asia, Australia, and North America were randomly assigned to either 90 μg/kg desmoteplase (n=60), 125 μg/kg desmoteplase (n=68), or placebo (n=65). Figure 1 shows the trial profile. Seven patients were randomised but not treated and they were not included in the analysis. 158 patients completed the study.

The study groups were well balanced with regard to baseline characteristics (table 1). The patients had an overall median age of 71·0–73·5 years, a stroke of mild to moderate severity (median baseline NIHSS score of 9 points), and most (63% [117 of 186]) were treated within 6–9 h of the onset of the symptoms of stroke. 66% (122 of 186) of patients were randomised

on the basis of MRI screening. 30% (53 of 179) had vessel occlusion (TIMI 0–1) at randomisation: 20% (12 of 61) on CT angiography and 35% (41 of 118) on MR angiography. The absolute core lesion volumes (overall median volume 10·6 cm^3) and mismatch volumes (overall median volume 52·5 cm^3) were small across the study groups. The relative mismatch volumes were high across the study groups, with an overall median of 530% (IQR 200% to 1700%).

There was no statistically significant difference in clinical outcome between the three groups. Table 2 shows the composite responder rate (clinical improvement) at day 90, as defined by the primary endpoint.

The proportion of patients with serious adverse events was 35% (20 of 57) for 90 μg/kg desmoteplase, 36% (24 of 66) for 125 μg/kg desmoteplase, and 29% (18 of 63) for placebo. The most common serious adverse events were ischaemic stroke (11% [20 of 186]), pneumonia (7% [12 of 186]), decreased haemoglobin (6% [11 of 186]), and intracranial haemorrhage (5% [10 of 186]).

Symptomatic intracranial haemorrhage within 72 h after treatment was observed in 4% (5 of 123) of patients in the desmoteplase groups—3·5% (2 of 57) in the 90 μg/kg group and 4·5% (3 of 66) in the 125 μg/kg group—and none of the placebo-treated patients. One of the two symptomatic intracranial haemorrhages in the 90 μg/kg desmoteplase group was due to worsening of a baseline haemorrhagic infarction, which constituted a serious protocol violation. The observations of symptomatic intracranial haemorrhage made by principal investigators matched the central blinded assessment except in one case, which was deemed as indeterminate (it met the protocol definitions of neither symptomatic nor asymptomatic) according to central assessment.

Asymptomatic intracranial haemorrhage was seen within 72 h of giving study medication in 35% (20 of 57) of patients treated with 90 μg/kg desmoteplase, 33% (22 of 66) of patients treated with 125 μg/kg desmoteplase, and 33% (21 of 63) of placebo-treated patients.

The application of the most conservative definition of the National Institute of Neurological Disorders and Stroke (NINDS) study criteria, in which acute neurological worsening of 1 point or more in the NIHSS is deemed relevant, the rates of symptomatic intracranial haemorrhage within 72 h of giving study medication were ·8% (5 of 57) for 90 μg/kg desmoteplase, 10·6% (7 of 66) for 125 μg/kg desmoteplase, and 14·3% (9 of 63) for placebo. By use of the ECASS II definition, in which bleeds that occur up to 7 days and are associated with a worsening of the NIHSS of 4 points are counted, the rate of symptomatic intracranial haemorrhage was 5·3% (3 of 57) for 90 μg/kg desmoteplase, 9·1% (6 of 66) for 125 μg/kg desmoteplase, and 4·8% (3 of 63) for placebo.

13 major haemorrhagic events were reported by 5% of patients (3 of 57) in the 90 μg/kg desmoteplase group, 8% (5 of 66) in the 125 μg/kg desmoteplase group, and 6% (4 of 63) in the placebo group. Three events, one in each study group, occurred within 24 h of study drug administration; 10 events occurred later than 72 h post-treatment. 21 deaths occurred within 90 days (11% overall mortality rate). Four patients died in the placebo group, three in the 90 μg/kg desmoteplase group, and 14 in the 125 μg/kg desmoteplase group. No anaphylactic reactions occurred.

In October, 2006, after 170 patients had been recruited, the data monitoring committee temporarily halted enrolment in the trial to investigate the increased frequency of deaths in the 125 μg/kg desmoteplase group. After a review of the unblinded data, the study was restarted on the recommendation of the data monitoring committee. Neither the details of the data

monitoring committee's unblinded review nor its rationale for halting the trial were discussed with the other study participants until after the database was locked.

A blinded adjudication of the causes of deaths in DIAS-2, done by members of the steering committee and the data monitoring committee after termination of the study, attributed four of the 14 deaths in the 125 μg/kg desmoteplase group to the index stroke (including three symptomatic intracranial haemorrhages), four to recurrent stroke and its complications, and the rest to miscellaneous reasons (table 3). Three deaths, all due to symptomatic intracranial haemorrhage, were assessed as causally related to desmoteplase and one death due to recurrent stroke was deemed as unlikely to be related. Thus, 11 of 14 deaths were adjudicated as death due to stroke or reasons unrelated to the study drug, with most being late deaths (figure 2). In general, patients who died in the study were older than those who survived (median age 79 years *vs* 72 years), had higher baseline NIHSS scores (median score 15 points *vs* 9 points), and had larger core lesion volumes on MRI (median volume 25·8 cm^3 *vs* 8·6 cm^3).

Comparison of baseline NIHSS scores, mismatch volumes, core lesion volumes, vessel occlusion, and age between the placebo and desmoteplase groups within each imaging subgroup (MRI and CT) showed no statistically significant differences (table 4). A comparison of the MRI and CT subgroups, however, showed a statistically significant difference for absolute and relative tissue at risk volume (higher in MRI; $p<0·0001$ and $p=0·0001$, respectively) and NIHSS score (higher in CT; $p=0·007$). Although low in both groups, the rate of vessel occlusion at baseline in patients who were assessed with CT was significantly lower than in the patients assessed with MRI (20% [12 of 61] *vs* 35% [41 of 118]; $p=0·04$). However, vessel occlusion at baseline was associated with higher NIHSS scores when assessed with CT than with MRI (median score 18·5 points *vs* 10·0 points).

The central assessment of baseline scans for randomised patients confirmed a qualifying mismatch in 88% (56 of 64) of CT-screened patients and in 84% (103 of 122) of MRI-screened patients. The non-confirmed cases had matched core and hypoperfusion (n=19), no perfusion abnormality (n=4), or were technically inadequate to assess (n=4).

There was no significant effect of treatment on core lesion volume. Patients treated with placebo showed a small decrease in core lesion volume between baseline and day 30 (median change –10·0% [–0·9 cm^3]), whereas patients treated with 90 μg/kg desmoteplase had an increase in core lesion volume of 14% (0·5 cm^3) and patients treated with 125 μg/kg desmoteplase had a 10·8% (0·3 cm^3) increase in core lesion volume. The patients who had the higher dose showed an inconsistent pattern, with an increase in core lesion volume of 43% (2·9 cm^3) in patients screened with MRI compared with a decrease of 44·7% (4·2 cm^3) in the patients screened with CT. The percentage changes have to be regarded with caution because of the small initial volumes. Irrespective of treatment assignment, patients with good clinical outcome were more likely to have no lesion growth, defined as any increase in lesion size (63% [46 of 73], 95% CI 51%–74%), whereas those with poor clinical outcome were more likely to have lesion growth (62% [53 of 86], 95% CI 51%–72%). The measurement of core lesion volume by the central image reading group showed greater inter-rater variability for CT than for MRI (inter-rater difference of >30% and >5 cm^3: 41% [26 of 64] for CT *vs* 10% [12 of 122] for MRI).

The clinical response rates in patients who qualified for the study on the basis of MRI were compared with those who qualified on the basis of CT. We found no statistically significant overall difference in response rates: 90 μg/kg desmoteplase MRI 54% [21 of 39] *vs* CT 33% [6 of 18]); 125 μg/kg desmoteplase MRI 38% [17 of 45] *vs* CT 33% [7 of 21]); placebo MRI 45% [17 of 38] *vs* CT 48% [12 of 25]. The difference between MRI and CT response rates for

the lower dose can be explained by an imbalance in baseline NIHSS scores (median 8 points [MRI] *vs* 12 points [CT]).

We also studied the effects of time from stroke onset to treatment and of sex. The clinical response rates in patients who were treated 3–6 h after stroke onset compared with those treated after 6–9 h were: 90 μg/kg desmoteplase 42% (8 of 19) versus 50% (19 of 38); 125 μg/kg desmoteplase 46% (11 of 24) versus 31% (13 of 42); and placebo 50% (13 of 26) versus 43% (16 of 37). Women generally had a worse outcome than men (90 μg/kg desmoteplase 43% [13 of 30] *vs* 52% [14 of 27]; 125 μg/kg desmoteplase 32% [12 of 37] *vs* 41% [12 of 29]; and placebo 38% [10 of 26] *vs* 51% [19 of 37]).

The clinical response rates in patients with vessel occlusion (TIMI 0–1) were assessed retrospectively: 90 μg/kg desmoteplase 36% (5 of 14); 125 μg/kg desmoteplase 27% (6 of 22); and placebo 18% (3 of 17). The corresponding rates in patients with no occlusion (TIMI 2–3 points) were: 90 μg/kg desmoteplase 50% (20 of 40); 125 μg/kg desmoteplase 40% (16 of 40); and placebo 57% (26 of 46).

Discussion

In contrast with the DIAS and DEDAS studies, DIAS-2 did not show a beneficial effect for either dose of desmoteplase given 3–9 h after the onset of stroke symptoms. The rate of symptomatic intracranial haemorrhage was consistent with the low rates seen in the DIAS and DEDAS studies. By applying the NINDS stroke trial definition, a higher rate of symptomatic intracranial haemorrhage was seen in the overall population, with no increased incidence in the patients who took desmoteplase compared with those who took placebo. The rates of symptomatic intracranial haemorrhage were comparable to those in the ECASS II study (when the same definition was applied) for the patients who received the higher dose of desmoteplase and significantly lower for those who received the lower dose, which suggests an improved safety profile compared with other studies of thrombolytic treatment (within both the early and late time windows).[1,16–18] However, the relatively high death rate in the high-dose group was an unexpected finding.

No significant imbalances were noted for patients' characteristics among the three treatment arms. An adjudication on the causes of death showed that only three deaths in the higher-dose group, all of which were associated with symptomatic intracranial haemorrhage, were causally related to desmoteplase. Furthermore, the patients who died were older, had higher baseline NIHSS scores, and larger infarct volumes than did the survivors, which indicates the presence of several comorbidities in the patients who died and therefore supports the possibility of an incidental accumulation of death within a small sample. This high death rate partly explains the low proportion of responders in the higher-dose group.

Despite having similar selection criteria, DIAS-2 differed from the DIAS and DEDAS studies in several ways (table 5). First, baseline strokes were less severe across all study groups in DIAS-2; the initial stroke severity was 9 points on the NIHSS, which is less than the observed median NIHSS score of 12 points at admission into DIAS and DEDAS.[10,11] NIHSS score at presentation is a major contributor and predictor of clinical outcome. The milder the initial stroke is, the better the spontaneous outcome. A difference of 2 to 3 points compared with the previous studies might explain most of the positive placebo response. Consequently, mild severity of stroke was associated with profoundly smaller core lesion volumes. The occurrence of initial proximal vessel occlusion, as assessed by MR angiography or CT angiography, was unexpectedly low. Overall, only 30% of the patients had proximal vessel occlusion, which contrasts with the occlusion rate observed in DIAS and DEDAS (combined rate 57%). Furthermore, although significantly more patients in DIAS and DEDAS were treated within

3–6 h in the placebo and higher-dose desmoteplase groups compared with patients in DIAS-2, a comparable distribution, with more patients treated late, was seen for the lower-dose desmoteplase group. The distribution of response rates in DIAS-2, however, does not enable any specific conclusion to be drawn with regard to the effect of time. By contrast with DIAS and DEDAS, there were more women in the desmoteplase groups in DIAS-2; more men were treated with placebo across all studies. Women had worse outcome than men in DIAS-2; however, this did not seem to influence the significantly worse outcome associated with both sexes in the higher dose group, nor the overall improved outcome for placebo compared with DIAS and DEDAS.

The low rate of proximal vessel occlusion translates into small infarct core and small absolute mismatch volume. The relative mismatch volumes seem to be a less sensitive predictor of improved outcome after thrombolysis. Despite the fact that they were significantly higher in DIAS-2 than in DIAS or DEDAS, this did not translate into an observable benefit. The small absolute mismatch volumes associated with the absence of major vessel occlusion might explain the absence of a desmoteplase effect compared with placebo. Analysis of the clinical response versus placebo in the subgroup of patients with a TIMI score of 0–1 showed a treatment effect of 18% for the lower dose of desmoteplase and 9% for the higher dose (partly owing to the relatively high death rate), whereas no treatment effect was seen in patients with TIMI 2–3.

DIAS-2 used MR PI–DWI and perfusion CT as selection criteria. Two main observations can be made in this respect. First, there were profound differences in mismatch volumes between MRI and CT; but the constraints associated with CT brain coverage in the context of this study might have contributed to this finding. Second, there were inconsistencies between MRI and CT data on the change in core lesion volume at day 30, particularly in the higher-dose desmoteplase group, in which a median percentage increase in core lesion volume on MRI was seen compared with a similar decrease on CT. As a result, whether the pooling of MRI and CT data can be justified is questionable.

Several factors might have masked or increased the difficulty of showing a potential beneficial effect of desmoteplase over placebo: the good prognosis of patients with mild stroke, the small core and mismatch lesion volumes associated with the absence of proximal cerebral vessel occlusion, and the inadequate sample size owing to an overly optimistic predicted effect size. Not only do imaging selection parameters need to be refined, but also simplistic notions of equivalence between perfusion MRI and perfusion CT might not be justified. Also, the complex inter-relationship between site and degree of vascular occlusion, collateral blood flow, tissue perfusion, mismatch imaging, and clinical outcomes require further investigation. The criteria to optimise the selection and treatment outcomes of patients with acute ischaemic stroke is elusive.

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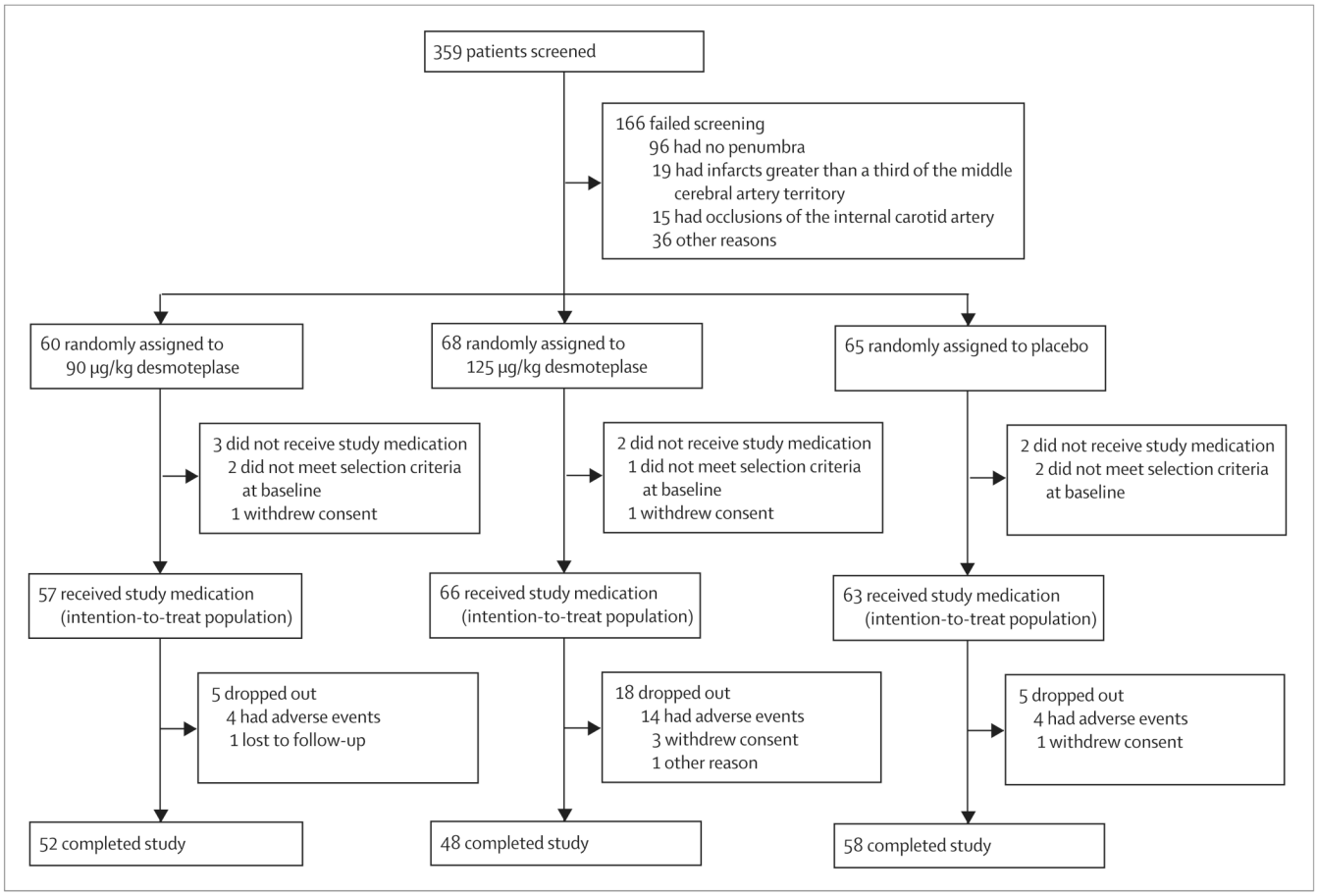

Figure 1. Trial profile

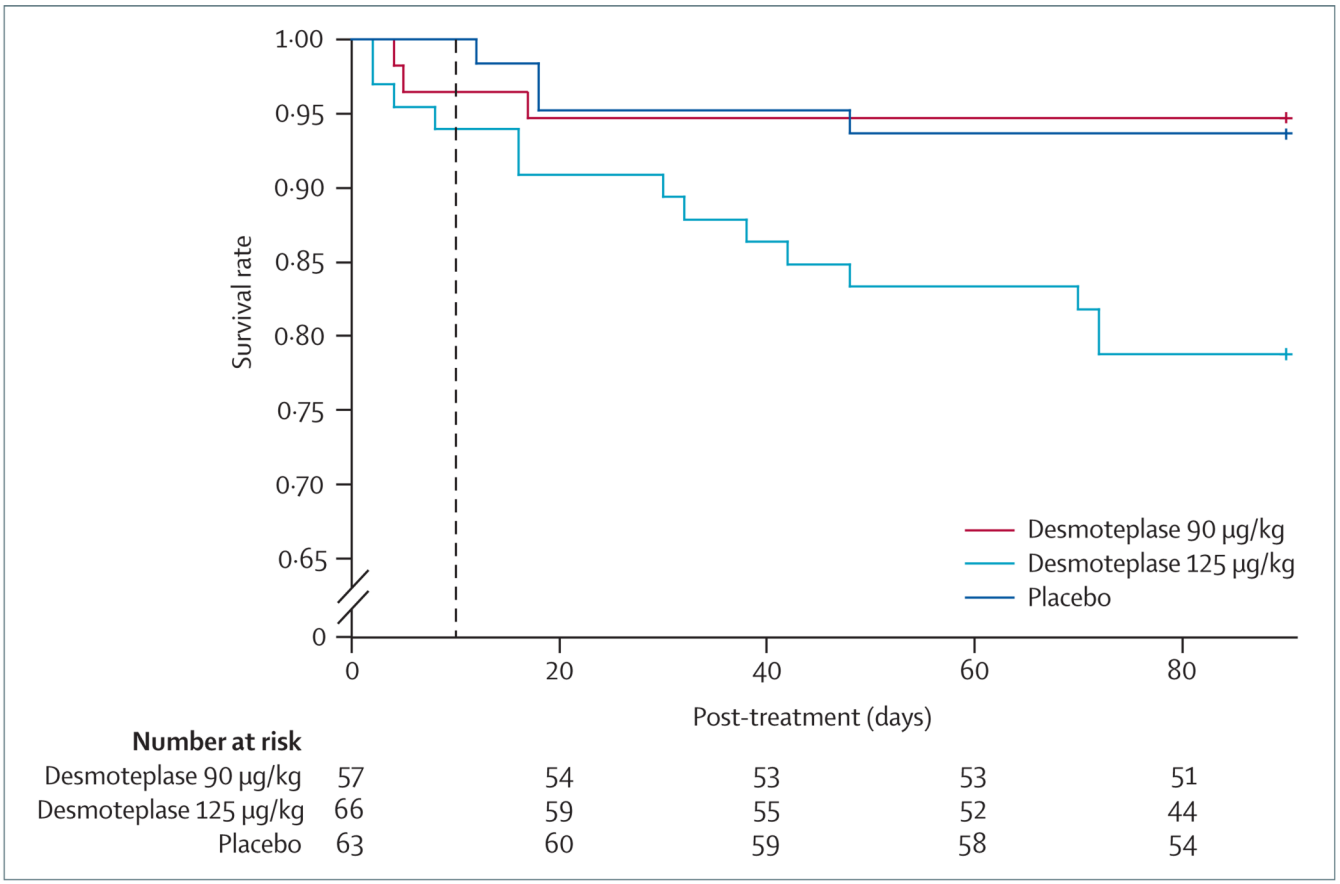

Figure 2. Kaplan–Meier estimates of survival

Note break in y axis. Broken line indicates 10-day post stroke interval, during which most stroke-related deaths occur.

Table 1

Characteristics of patients at baseline

	90 µg/kg desmoteplase (n=57)	125 µg/kg desmoteplase (n=66)	Placebo (n=63)
Age (years)	67.9 (13.4); 71.0 (61 to 78)	70.0 (12.3); 73.5 (63 to 80)	70.0 (14.0); 73.0 (62 to 80)
Men	27 (47%)	29 (44%)	37 (59%)
Diabetes	16 (28%)	15 (23%)	12 (19%)
Time to treatment (min)	388 (88); 394 (300 to 456)	402 (88); 383 (335 to 483)	391 (92); 383 (321 to 460)
Time elapsed since onset of symptoms (h)			
3–6	19 (33%)	24 (36%)	26 (41%)
>6–9	38 (67%)	42 (64%)	37 (59%)
NIHSS score	10.7 (5.6); 9 (7 to 14)	10.4 (4.6); 9 (7 to 15)	10.3 (5.0); 9 (6 to 14)
Prestroke mRS score			
0	46 (81%)	57 (86%)	52 (83%)
1	11 (19%)	9 (14%)	11 (18%)
Vessel occlusion TIMI score 0–1*	14 (26%)	22 (36%)	17 (27%)
Imaging modality			
MRI	39 (68%)	45 (68%)	38 (60%)
CT	18 (32%)	21 (32%)	25 (40%)
Mismatch volume (cm^3)	83.3 (80.2); 51.9 (25 to 127)	87.0 (70.4); 66.2 (32 to 138)	75.8 (72.6); 48.8 (26 to 106)
Mismatch volume (%)	3400 (14 000); 510 (120 to 1700)	4200 (12 000); 530 (210 to 2400)	1400 (2900); 480 (220 to 1500)
Core lesion volume (cm^3)	21.3 (32.0); 7.9 (3 to 25)	17.6 (17.7); 11.3 (3 to 31)	16.2 (17.1); 12.3 (4 to 20)

Data are mean (SD), median (IQR), or number (%). TIMI=thrombosis in myocardial infarction.

*Patients with TIMI assessment available: 90 µg/kg (n=54); 125 µg/kg (n=62); placebo (n=63).

Table 2

Primary effi cacy endpoint (composite responder rate at day 90) in the intention-to-treat population

	Desmoteplase 90 μg/kg (n=57)	Desmoteplase 125 μg/kg (n=66)	Placebo (n=63)	p value (global test)
Composite responder rate	27 (47%)	24 (36%)	29 (46%)	0.47
Individual component responder rate				
NIHSS ≤1 or improvement ≥8 points	33 (58%)	33 (50%)	37 (59%)	..
mRS score 0–2	31 (54%)	32 (49%)	36 (57%)	..
Barthel index 75–100	39 (68%)	36 (55%)	42 (67%)	..

NIHSS=National Institutes of Health stroke scale. mRS=modifed Rankin scale.

Table 3

Mortality within 90 days

	Time between study medication and death (days)	Relation to trial medication
Placebo: four deaths (6%)		
Recurrent stroke with herniation	18	NA
Large index stroke with possible aspiration pneumonia and sepsis	12	NA
Aspiration pneumonia with possible sepsis	48	NA
Aspiration pneumonia with possible sepsis	18	NA
Desmoteplase 90 μg/kg: three deaths (5%)		
Large index stroke with mass effect and cardiopulmonary arrest	5	Unrelated
ICH	4	Related
Ischaemic heart disease	17	Unrelated
125 μg/kg desmoteplase: 14 deaths (21%)		
Herniation from recurrent stroke	2	Unlikely
Complication of IA intervention for recurrent stroke	16	Unrelated
Sepsis after recurrent stroke	72	Unrelated
Recurrent stroke	72	Unrelated
Index stroke and multiorgan failure	32	Unrelated
Herniation secondary to ICH	16	Related
ICH with herniation	8	Related
ICH with herniation	2	Related
Bowel infarction	42	Unrelated
Gastrointestinal bleeding	38	Unrelated
Cardiopulmonary arrest after myocardial infarction	4	Unrelated
Pulmonary embolism	70	Unrelated
Sepsis from urinary tract infection	48	Unrelated
Cardiac failure	30	Unrelated

NA=not applicable. ICH=intracranial haemorrhage. IA=intra-arterial.

Table 4

Selected baseline characteristics that potentially predict a clinical response by imaging modality (MRI *vs* CT)

	MRI			CT			MRI versus CT (p value)
	Desmoteplase 90 µg/kg (n=39)	**Desmoteplase 125 µg/kg (n=45)**	**Placebo (n=38)**	**Desmoteplase 90 µg/kg (n=18)**	**Desmoteplase 125 µg/kg (n=21)**	**Placebo (n=25)**	
Age (years)	68.7 (13.0);	68.8 (12.3);	70.5 (13.3);	66.2 (14.5);	72.7 (12.1);	69.2 (15.2);	0.63
	72.0 (61 to 78)	70.0 (63 to 79)	73.5 (64 to 80)	69.0 (60 to 78)	76.0 (69 to 81)	72.0 (58 to 80)	
p value	0.57	0.69		0.54	0.40		
NIHSS	9.6 (4.9);	10.1 (4.8);	9.5 (4.5);	13.2 (6.1);	11.2 (4.3);	11.6 (5.5);	0.007
	8.0 (6 to 13)	9.0 (6 to 13)	9.0 (6 to 14)	12.0 (8 to 16)	10.0 (8 to 15)	10.0 (7 to 17)	
p value	0.99	0.68		0.36	0.76		
Mismatch volume (cm^3)	102.3 (86.9);	108.3 (73.5);	104.8 (79.8);	41.8 (40.3);	46.5 (41.3);	32.4 (23.8);	<0.0001
	56.4 (34 to 186)	109.2 (47 to 161)	74.1 (43 to 168)	29.3 (12 to 66)	39.9 (11 to 64)	28.0 (14 to 48)	
p value	0.89	0.97		0.18	0.17		
Mismatch volume (%)	4800 (17 000);	5100 (15 000);	1500 (1800);	510 (660);	2400 (5500);	1300 (4100);	0.0001
	800 (230 to 2500)	740 (250 to 2700)	1200 (290 to 1700)	150 (50 to 960)	500 (120 to 1300)	230 (110 to 640)	
p value	0.25	0.18		0.40	0.36		
Vessel occlusion*TIMI 0–1	11 (29%)	18 (43%)	12 (32%)	3 (19%)	4 (20%)	5 (20%)	0.04
p value	0.77	0.33		0.95	1.000		
Core lesion volume (cm^3)	19.3 (32.0);	17.2 (16.7);	12.4 (9.9);	26.2 (32.5);	18.4 (20.3);	22.2 (23.6);	0.57
	6.8 (3 to 20)	11.7 (3 to 24)	10.8 (6 to 17)	15.0 (3 to 39)	10.9 (1 to 32)	17.1 (2 to 32)	
p value	0.20	0.14		0.46	0.51		

Data are mean (SD), median (IQR), or number (%). NIHSS=National Institutes of Health stroke scale.

*Patients with available TIMI assessment (MRI *vs* CT): 90 µg/kg (n=38 *vs* 16); 125 µg/kg (n=42 *vs* 20); placebo (n=38 *vs* 25).

Table 5

Comparison of baseline characteristics: DIAS/DEDAS versus DIAS-2

	Desmoteplase 90 µg/kg		Desmoteplase 125 µg/kg		Placebo		DIAS/DEDAS *vs* DIAS-2
	DIAS/DEDAS (n=29)	**DIAS-2 (n=57)**	**DIAS/DEDAS (n=30)**	**DIAS-2 (n=66)**	**DIAS/DEDAS (n=35)**	**DIAS-2 (n=63)**	**p value**
NIHSS	11.6 (4.4); 11 (8 to 15)	10.7 (5.6); 9 (7 to 14)	11.1 (4.9); 11 (7 to 16)	10.4 (4.6); 9 (7 to 15)	11.8 (4.5); 12 (8 to 16)	10.3 (5.0); 9 (6 to 14)	0.053
Men	15 (52%)	27 (47%)	16 (53%)	29 (44%)	19 (54%)	37 (59%)	0.70
Core lesion volume (cm^3)	35.8 (26.0); 27.6 (14 to 53)	21.3 (32.0); 7.9 (3 to 25)	40.1 (36.6); 22.1 (13 to 68)	17.6 (17.7); 11.3 (3 to 31)	30.1 (25.4); 23.5 (10 to 47)	16.2 (17.1); 12.3 (4 to 20)	<0.0001
Mismatch volume (cm^3)	117.4 (117.4); 113.9 (13 to 195)	83.3 (80.2); 51.9 (25 to 127)	133.6 (90.9); 129.9 (44 to 219)	87.0 (70.4); 66.2 (32 to 138)	115.1 (101.7); 99.2 (23 to 205)	75.8 (72.6); 48.8 (26 to 106)	0.008
Mismatch volume (%)	550 (650); 310 (50 to 870)	3400 (14 000); 510 (120 to 1700)	950 (1400); 240 (160 to 1400)	4200 (12 000); 530 (210 to 2400)	540 (670); 270 (75 to 730)	1400 (2900); 480 (220 to 1500)	0.002
Vessel occlusion*							
TIMI 0–1	15 (54%)	14 (26%)	16 (59%)	22 (36%)	20 (59%)	17 (27%)	0.0001
Time since stroke onset							
3–6 h	6 (21%)	19 (33%)	19 (63%)	24 (36%)	23 (66%)	26 (41%)	0.03

Data are mean (SD), median (IQR), or number (%). DIAS/DEDAS=Desmoteplase In Acute ischemic Stroke/Dose Escalation study of Desmoteplase in Acute ischemic Stroke phase II studies.

*Patients with available TIMI assessment (DIAS/DEDAS *vs* DIAS-2): 90 µg/kg (n=28 *vs* 54); 125 µg/kg (n=27 *vs* 62); and placebo (n=34 *vs* 63).