

Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS)

Evidence of Safety and Efficacy 3 to 9 Hours After Stroke Onset

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Background and Purpose—Desmoteplase is a novel plasminogen activator with favorable features in vitro compared with available agents. This study evaluated safety and efficacy of intravenous (IV) desmoteplase in patients with perfusion/diffusion mismatch on MRI 3 to 9 hours after onset of acute ischemic stroke.

Methods—DEDAS was a placebo-controlled, double-blind, randomized, dose-escalation study investigating doses of 90 $\mu\text{g}/\text{kg}$ and 125 $\mu\text{g}/\text{kg}$ desmoteplase. Eligibility criteria included baseline National Institute of Health Stroke Scale (NIHSS) scores of 4 to 20 and MRI evidence of perfusion/diffusion mismatch. The safety end point was the rate of symptomatic intracranial hemorrhage. Primary efficacy co-end points were MRI reperfusion 4 to 8 hours after treatment and good clinical outcome at 90 days. The primary analyses were intent-to-treat. Before unblinding, a target population, excluding patients violating specific MRI criteria, was defined.

Results—Thirty-seven patients were randomized and received treatment (intent-to-treat; placebo: $n=8$; 90 $\mu\text{g}/\text{kg}$: $n=14$; 125 $\mu\text{g}/\text{kg}$: $n=15$). No symptomatic intracranial hemorrhage occurred. Reperfusion was achieved in 37.5% (95% CI [8.5; 75.5]) of placebo patients, 18.2% (2.3; 51.8) of patients treated with 90 $\mu\text{g}/\text{kg}$ desmoteplase, and 53.3% (26.6; 78.7) of patients treated with 125 $\mu\text{g}/\text{kg}$ desmoteplase. Good clinical outcome at 90 days occurred in 25.0% (3.2; 65.1) treated with placebo, 28.6% (8.4; 58.1) treated with 90 $\mu\text{g}/\text{kg}$ desmoteplase and 60.0% (32.3; 83.7) treated with 125 $\mu\text{g}/\text{kg}$ desmoteplase. In the target population ($n=25$), the difference compared with placebo increased and was statistically significant for good clinical outcome with 125 $\mu\text{g}/\text{kg}$ desmoteplase ($P=0.022$).

Conclusions—Treatment with IV desmoteplase 3 to 9 hours after ischemic stroke onset appears safe. At a dose of 125 $\mu\text{g}/\text{kg}$ desmoteplase appeared to improve clinical outcome, especially in patients fulfilling all MRI criteria. The results of DEDAS generally support the results of its predecessor study, Desmoteplase in Acute Ischemic Stroke (DIAS). (*Stroke*. 2006;37:1227-1231.)

Key Words: desmoteplase ■ stroke ■ thrombolytic therapy

Intravenous (IV) thrombolytic treatment of acute ischemic stroke is currently limited to recombinant tissue plasminogen activator (rt-PA) within 3 hours after symptom onset.¹ A pooled analysis of all IV rt-PA stroke studies suggests a benefit for treatment delays of up to 4.5 hours.² All of these studies used routine brain computed tomography (CT) for patient selection.

Newer imaging technologies suggest that salvageable brain may be present for several hours in many patients with acute stroke.³⁻⁶ Desmoteplase (rDSPA α 1) is a novel plasminogen activator with favorable features compared with available agents including high fibrin specificity, long half life, and

lack of neurotoxicity or β -amyloid activation in animal models of stroke.⁷⁻⁹ The Desmoteplase in Acute Ischemic Stroke Study (DIAS)¹⁰ was the first clinical study to select patients for IV thrombolysis up to 9 hours after stroke onset based on mismatch of perfusion-weighted/diffusion-weighted (DWI) MRI. DIAS reported a low rate of symptomatic intracranial hemorrhage (sICH) and evidence of reperfusion and clinical efficacy using this agent and imaging approach. The Dose Escalation of Desmoteplase in Acute Stroke (DEDAS) study further evaluated safety and efficacy of IV desmoteplase in patients with perfusion/diffusion mismatch 3 to 9 hours after stroke onset.

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Patients and Methods

Methods and procedures of DEDAS were largely identical to DIAS.¹⁰ Specifics of DEDAS and a brief overview are reported here.

Patients and Desmoteplase Dosages

Between March 2003 and October 2004, 21 centers in the US and 4 centers in Germany participated in DEDAS. The protocol and all amendments received Institutional Review Board approval at each center, and written informed consent was obtained from all patients or their legal representatives.

DEDAS was a randomized, placebo-controlled, bodyweight-adjusted dose-escalation study. Doses of 90 $\mu\text{g}/\text{kg}$ and 125 $\mu\text{g}/\text{kg}$ desmoteplase were evaluated. Each dose tier included 15 desmoteplase patients and 4 placebo patients. The sample size per dose tier was fixed as α 0.20 (probability of falsely regarding desmoteplase as unsafe) and β 0.40 (power of 60% for detecting an unacceptably high rate of ICH >20%). No stratification was implemented. An independent Data Monitoring Committee (IDMC) monitored hemorrhages and other adverse events using prospectively defined stopping rules. Progression to the next dose tier was based on the recommendation of the IDMC.

Patients were randomized to desmoteplase or placebo via an interactive voice response system. Study drug was administered as an IV bolus over 1 to 2 minutes. The IDMC was immediately informed of each newly randomized patient, any hemorrhages, and the 72-hour outcome of each patient. It was unblinded and not involved in other study tasks.

Main Inclusion Criteria

Criteria included subjects age 18 through 85 years, and stroke onset was within 3 through 9 hours; baseline National Institute of Health Stroke Scale (NIHSS) score was 4 through 20. There was at least 20% perfusion/diffusion mismatch with a perfusion deficit, with or without DWI lesion, of >2 cm in diameter and involving the cerebral cortex on baseline. MRI inclusion was based on investigator visual readings of MRI; quantitative analyses of lesion volume were based on blinded central imaging readings (Perceptive Informatics, Inc). Briefly, perfusion-weighted imaging and DWI sequences were obtained in DICOM format and converted for planimetric analysis using ALICE software. Lesion borders were drawn and volumes were then calculated for the entire lesion. (A comprehensive description of MRI acquisition and analyses will be separately communicated.)

Exclusion criteria were similar to those adopted by other thrombolytic studies including any hemorrhage on baseline CT. Internal carotid artery (ICA) occlusions without coexisting separate occlusion of the middle cerebral artery were excluded, because of the difficulty distinguishing between chronic and acute ICA lesions in such patients.

Imaging Examinations

MRI was performed at screening, 4 to 8 hours post-treatment and at 30 days follow-up. CT was performed at 24 hours in all patients to document any intracranial bleeding.

Safety End Points

The primary safety end point was the rate of sICH, defined as any CT-confirmed ICH associated with a worsening of ≥ 4 points on the NIHSS within 72 hours of treatment. Other safety outcomes included mortality, anaphylaxis and major systemic bleeding, defined as a bleeding considered life-threatening, the requirement to administer 2 or more units of packed red blood cells or a hemoglobin-drop by 40 g/L or more. Other adverse events and serious adverse events were also monitored.

Efficacy End Points

The coprimarily efficacy end points were reperfusion at 4 to 8 hours and clinical outcome at 90 days. Physiologically relevant reperfusion was defined as either $\geq 30\%$ reduction of mean-transit-time volume of abnormality or ≥ 2 points improvement on the adapted Thrombolysis in Myocardial Infarction (TIMI) scale on magnetic resonance angiography. Good clinical outcome was a composite end point defined as ≥ 8 points improvement or scoring 0 to 1 on the NIHSS, a score of 0 to 2 on the modified Rankin Scale, and a Barthel Index score of 75 to 100 at 90 days.

Analyses

The primary analysis was intent-to-treat (ITT). In addition, a target population (TP) was defined before unblinding, which included only patients who had MRI mismatch and no isolated ICA occlusion as determined by the core laboratory.

Concomitant Medication

In the first 24 hours after administration of study drug, anticoagulants and antiplatelet agents were not allowed. Use of other thrombolytics was prohibited in the first 72 hours.

Results

The ITT population comprised 37 patients who were randomized and received treatment with study drug (placebo $n=8$, desmoteplase 90 $\mu\text{g}/\text{kg}$ $n=14$, desmoteplase 125 $\mu\text{g}/\text{kg}$ $n=15$). One additional patient was withdrawn after randomization but before drug administration because of nonfulfillment of MRI criteria.

The desmoteplase and placebo groups were balanced with regard to age but not for time after onset (longer in the 90 $\mu\text{g}/\text{kg}$ dose group), baseline DWI lesion volumes (larger in placebo), and baseline NIHSS (highest in placebo; Table 1). Stroke etiologies were similar in all subgroups.

Twelve randomized patients were later determined by the central imaging laboratory to have violated MRI criteria. Six patients had isolated ICA occlusion and another 6 had either no mismatch or no perfusion deficit. Six violations occurred in the 90 $\mu\text{g}/\text{kg}$ dose group, 4 in the 125 $\mu\text{g}/\text{kg}$ group, and 2 in placebo. Hence, the TP sample size was $n=6$ for placebo, $n=8$ for 90 $\mu\text{g}/\text{kg}$ and $n=11$ for 125 $\mu\text{g}/\text{kg}$ (in total: $n=25$).

TABLE 1. Characteristics of Patients (ITT population)

	Placebo, (n=8)	Desmoteplase 90 $\mu\text{g}/\text{kg}\ddagger$, (n=14)	Desmoteplase 125 $\mu\text{g}/\text{kg}\ddagger$, (n=15)	Desmoteplase \ddagger , (n=29)	Total, (n=37)
Female*	37.5%	42.9%	46.7%	44.8%	43.2%
Age \ddagger , y	71.5 [42–85]	74.5 [57–85]	72 [42–84]	73 [42–85]	73 [42–85]
NIHSS \ddagger	12 [6–18]	10 [4–18]	9 [5–19]	9 [4–19]	11 [4–19]
Time after onset \ddagger , min	443 [220–516]	477 [393–568]	420 [222–531]	449 [222–568]	446 [220–568]
DWI lesion volume \ddagger , mL	35.1 [1.5–68.6]	25.3 [1.6–73.0]	20.7 [4.1–78.1]	22.2 [1.6–78.1]	22.7 [1.5–78.1]
Glucose level \ddagger , mmol/L	6.16 [5.66–9.05]	6.27 [5.44–15.76]	6.16 [5.44–15.76]	6.27 [4.66–15.76]	6.27 [4.66–15.76]

*Proportion of patients; \ddagger Median [Range]; \ddagger All values not significantly different from placebo.

Safety

Primary Safety End Point

No symptomatic ICHs were observed.

Other Safety End Points

Three deaths occurred within 90 days, 1 from each treatment group. The placebo patient died at day 5 secondary to stroke progression. The patient in the 90 $\mu\text{g}/\text{kg}$ group died at day 53 secondary to an aspiration pneumonia. The patient in the 125 $\mu\text{g}/\text{kg}$ group experienced evolution of left middle cerebral artery infarction with neurological deterioration complicated by pneumonia and died at day 15.

Twelve asymptomatic ICH were observed: in 12.5% of placebo-treated patients ($n=1$), and 35.7% ($n=5$) and 40.0% ($n=6$) of patients treated with 90 $\mu\text{g}/\text{kg}$ or 125 $\mu\text{g}/\text{kg}$, respectively. Nine were present on the routine 24-hour CT, 2 on delayed 24-hour CT before 72 hours and 1 on an unscheduled CT on day 15. Major systemic hemorrhage occurred in 12.5% ($n=1$) of placebo patients and 14.3% ($n=2$) and 13.3% ($n=2$) of patients treated, respectively, with 90 $\mu\text{g}/\text{kg}$ and 125 $\mu\text{g}/\text{kg}$ desmoteplase. Six of 11 asymptomatic ICH occurred in patients with MRI violations. No anaphylactic reactions occurred (Table 2).

Efficacy

Reperfusion (ITT)

MR images of 3 patients treated with 90 $\mu\text{g}/\text{kg}$ desmoteplase were either missing or not assessable. Early reperfusion at 4 to 8 hours after treatment occurred in 3 placebo-treated patients (37.5%), in 2 patients (18.2%) in the 90 $\mu\text{g}/\text{kg}$ group, and in 8 patients (53.3%) in the 125 $\mu\text{g}/\text{kg}$ group (Table 3, Figure, a); neither of the desmoteplase groups reached statistical superiority over placebo.

Primary Clinical End Point (ITT)

Good outcome at 90 days occurred in 2 (25.0%), 4 (28.2%) and 9 (60.0%) patients in the placebo, 90 $\mu\text{g}/\text{kg}$ and 125 $\mu\text{g}/\text{kg}$ desmoteplase groups, respectively (Table 3, Figure, a). The clinical outcome in the 125 $\mu\text{g}/\text{kg}$ group showed a trend

toward superiority over placebo (odds ratio [OR]=4.50; 95% CI: 0.67; 30.23; $P=0.06$).

TP: Reperfusion

Compared with the ITT population, the reperfusion rate in the TP increased for the 125 $\mu\text{g}/\text{kg}$ group (63.6%, $n=7$), but decreased for placebo (33.3%, $n=2$) and for 90 $\mu\text{g}/\text{kg}$ (16.7%, $n=1$). The higher reperfusion rate of the 125 $\mu\text{g}/\text{kg}$ group did not reach statistical significance over placebo (OR=3.50; 95% CI: 0.43; 28.45; $P=0.12$ (Table 3, Figure, b).

Among patients with MRI protocol violations, the overall reperfusion rate was 27.3% (1 of 2 in the placebo group; 1 of 5 in the desmoteplase 90 $\mu\text{g}/\text{kg}$ group and 1 of 4 in the 125 $\mu\text{g}/\text{kg}$ group).

TP: Primary Clinical End Point

The rate of good clinical outcome increased for the desmoteplase groups, 37.5% ($n=3$) for 90 $\mu\text{g}/\text{kg}$ and 72.7% ($n=8$) for the 125 $\mu\text{g}/\text{kg}$ group, but decreased for placebo (16.7%, $n=1$) when MRI violators were excluded. In the TP, clinical outcome in the 125 $\mu\text{g}/\text{kg}$ group was statistically superior to placebo (OR=13.33; 95% CI: 1.07; 166.37; $P=0.022$) but not in the 90 $\mu\text{g}/\text{kg}$ group (OR=3.00; 95% CI: 0.23; 39.61; $P=0.20$; Table 3, Figure, b).

Among patients with MRI protocol violations, a good clinical outcome was observed in 1 of 2 receiving placebo, and in 20.0% of patients treated with desmoteplase (1 of 6 receiving 90 $\mu\text{g}/\text{kg}$ and 1 of 4 receiving 125 $\mu\text{g}/\text{kg}$).

Additional Analyses: Time Window

There was a positive correlation (Spearman $\rho=0.35$; $P=0.03$) between baseline NIHSS and time from symptom onset, mainly caused by a few less severe strokes in the 3- to 6-hour time window, in the desmoteplase 125 $\mu\text{g}/\text{kg}$ group. The majority of patients, however, were randomized in the 6- to 9-hour window ($n=28$). Analysis restricted to the 6- to 9-hour window showed a random distribution of stroke severity (Spearman $\rho=0.08$) and eliminated the imbalance in baseline NIHSS and DWI lesion volume. A separate 3- to 6-hour analysis was not done attributable to the small ($n=9$) sample

TABLE 2. Safety (ITT population)

	Placebo, ($n=8$)	Desmoteplase 90 $\mu\text{g}/\text{kg}$, ($n=14$)	Desmoteplase 125 $\mu\text{g}/\text{kg}$, ($n=15$)	Desmoteplase, ($n=29$)	Total, ($n=37$)
Symptomatic ICH*†	0 (0; [0; 36.9])	0 (0; [0; 23.2])	0 (0; [0; 21.8])	0 (0; [0; 11.9])	0 (0; [0; 9.5])
Asymptomatic ICH*	1 (12.5; [0.3; 52.7])	5 (35.7; [12.8; 64.9])	6 (40.0; [16.3; 67.7])	11 (37.9; [20.7; 57.7])	12 (32.4; [18.0; 49.8])
OR vs placebo†		3.89 [0.37; 41.32] $P=0.13$	4.67 [0.45; 48.26] $P=0.098$	4.28 [0.46; 39.6] $P=0.100$	
Mortality*	1 (12.5; [0.3; 52.7])	1 (7.1; [0.2; 33.9])	1 (6.7; [0.2; 31.9])	2 (6.9; [0.8; 22.8])	3 (8.1; [1.7; 21.9])
OR vs placebo†		0.54 [0.03; 9.99] $P=0.66$	0.50 [0.03; 9.24] $P=0.68$	0.52 [0.04; 6.58] $P=0.69$	
Major systemic bleeding*	1 (12.5; [0.3; 52.7])	2 (14.3; [1.8; 42.8])	2 (13.3; [1.7; 40.5])	4 (13.8; [3.9; 31.7])	5 (13.5; [4.5; 28.8])
OR vs placebo†		1.17 [0.09; 15.32] $P=0.45$	1.08 [0.08; 14.08] $P=0.48$	1.12 [0.11; 11.70] $P=0.46$	
Anaphylactic reaction*‡	0 (0; [0; 36.9])	0 (0; [0; 23.2])	0 (0; [0; 21.8])	0 (0; [0; 11.9])	0 (0; [0; 9.5])

*No. of patients (%; [95% CI]); †OR; [95% CI]; P value (OR<1); ‡No OR calculated (division by 0).

TABLE 3. Efficacy

	Reperfusion 4–8 hours After Treatment*									
	Placebo		Desmoteplase 90 μg/kg		Desmoteplase 125 μg/kg		Desmoteplase		Total	
	ITT n=8	TP n=6	ITT n=11	TP n=6	ITT n=15	TP n=11	ITT n=26	TP n=17	ITT n=34	TP n=23
No. (%)	3 (37.5)	2 (33.3)	2 (18.2)	1 (16.7)	8 (53.3)	7 (63.6)	10 (38.5)	8 (47.1)	13 (38.2)	10 (43.5)
[95% CI]	[8.5; 75.5]	[4.3; 77.7]	[2.3; 51.8]	[0.4; 64.1]	[26.6; 78.7]	[30.8; 89.1]	[20.2; 59.4]	[23.0; 72.2]	[22.2; 56.4]	[23.2; 65.5]
OR vs placebo			0.37	0.40	1.90	3.50	1.04	1.78		
[95% CI]			[0.05; 3.01]	[0.03; 6.18]	[0.33; 11.01]	[0.43; 28.45]	[0.20; 5.34]	[0.25; 12.45]		
P value (OR<1)			P=0.82	P=0.74	P=0.24	P=0.12	P=0.48	P=0.28		
	Good Clinical Outcome 90 Days After Treatment†									
	n=8	n=6	n=14	n=8	n=15	n=11	n=29	n=19	n=37	n=25
No. (%)	2 (25.0)	1 (16.7)	4 (28.6)	3 (37.5)	9 (60.0)	8 (72.7)	13 (44.8)	11 (57.9)	15 (40.5)	12 (48.0)
[95% CI]	[3.2; 65.1]	[0.4; 64.1]	[8.4; 58.1]	[8.5; 75.5]	[32.3; 83.7]	[39.0; 94.0]	[26.4; 64.3]	[33.5; 79.7]	[24.8; 57.9]	[27.8; 68.7]
OR vs placebo			1.20	3.00	4.50	13.33	2.44	6.88		
[95% CI]			[0.17; 8.66]	[0.23; 39.61]	[0.67; 30.23]	[1.07; 166.4]	[0.42; 14.16]	[0.67; 70.82]		
P value (OR<1)			P=0.43	P=0.20	‡P=0.061	‡‡P=0.022	P=0.16	P=0.053		

*Patients with assessable images; Reperfusion defined as ≥30% reduction in MTT volume of abnormality OR ≥2 points improvement on adapted TIMI scale. †Good Outcome defined as ≥8 points NIHSS improvement (or final value ≤1) AND modified Rankin Scale ≤2 AND Barthel Index ≥75; ‡trend towards statistical superiority over placebo (efficacy 4.5× higher than placebo); ‡‡statistical superiority over placebo.

size. Reperfusion and good clinical outcome were observed in 62.5% (5 of 8) and 50.0% (4 of 8) of patients who received desmoteplase 125 μg/kg 6 to 9 hours after symptom onset despite a higher median baseline NIHSS (14) and age (median age=77.5 years) compared with the ITT (3 to 9 hours) group.

Change in Lesion Volume

Median T2 lesion volume increased in all treatment groups from baseline to day 30. The median increase in lesion

volume was smallest in the desmoteplase 125 μg/kg group (28.6%), but was not significantly different from the median increase (39.2%) in placebo patients.

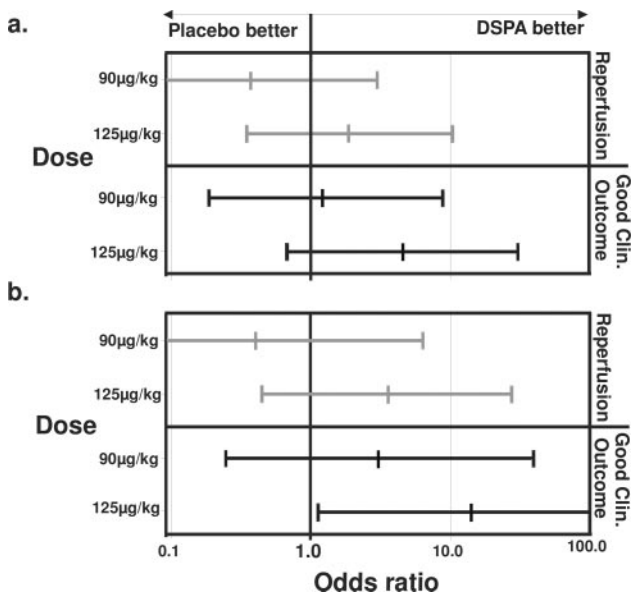
Reperfusion and Clinical Outcome

Reperfusion was highly correlated with good clinical outcome. In the 34 patients with assessable MR images, 69.2% (9/13) of patients with reperfusion had a good clinical outcome at 90 days compared with 19.0% (4/21) without reperfusion (P=0.003).

Discussion

DEDAS provides further evidence that IV thrombolysis with desmoteplase 3 to 9 hours after stroke onset at doses of 90 μg/kg and 125 μg/kg is safe with a low rate of sICH in patients selected by perfusion/diffusion mismatch on MRI. Reperfusion on MRI was strongly correlated with good clinical outcome and appeared improved with 125 μg/kg IV desmoteplase.

The in vitro properties of desmoteplase theoretically contribute to a low rate of sICH, enhanced reperfusion and possibly a low rate of reocclusion. Perfusion brain imaging further helps to optimize safety and patient selection for thrombolysis beyond 3 hours after stroke onset. The results of DIAS,¹⁰ supported now by DEDAS, are consistent with these hypotheses. In the combined studies there has been only 1 sICH out of 59 patients treated with either 90 μg/kg or 125 μg/kg desmoteplase, whereas MRI has provided physiological evidence of reperfusion efficacy, especially with 125 μg/kg. The rate of asymptomatic ICH, often a marker of reperfusion,¹¹ was increased in desmoteplase patients but was consistent with other thrombolysis studies, including DIAS.¹⁰



Univariate ORs over placebo regarding reperfusion (gray bars) and good clinical outcome after 90 days (black bars). a, Results of the ITT population. b, Results of the TP.

As opposed to DIAS,¹⁰ in DEDAS reperfusion in desmoteplase patients did not reach statistical significance compared with placebo although there was a strong trend with 125 $\mu\text{g}/\text{kg}$. The absence of reperfusion in the 90 $\mu\text{g}/\text{kg}$ group (18.2%) is also discordant with DIAS (46.7%). These differences may relate to the higher reperfusion rate in the placebo group in DEDAS (37.5%) compared with DIAS (19.2%) which might reflect the small sample size, or differences in sites of occlusion and collateral flow between the 2 studies. The higher rates of nonassessable images and MRI protocol violations in DEDAS may also have impacted on the 90 $\mu\text{g}/\text{kg}$ results. Detailed combined imaging analyses will be reported separately.

For clinical outcome, there was no difference between placebo and the 90 $\mu\text{g}/\text{kg}$ dose. Clinical outcome in the 125 $\mu\text{g}/\text{kg}$ group was substantially better than placebo (ITT: 35% absolute difference), reaching the level of DIAS. Again, statistical significance was not reached possibly because of the small sample size. The clinical response rate of the 125 $\mu\text{g}/\text{kg}$ group in DEDAS may also represent an overestimation attributable to an excess of less severely affected patients compared with placebo. However, the NIHSS imbalance was not present when the analysis was restricted to the 6- to 9-hour time window, yet the improved clinical outcome for the 125 $\mu\text{g}/\text{kg}$ group relative to placebo remained. The TP analysis also provides supporting evidence for the main study hypotheses. Reperfusion and clinical response rates of the target patients treated with 125 $\mu\text{g}/\text{kg}$ desmoteplase increased compared with ITT, whereas the response rates of the MRI protocol violators treated with desmoteplase were low. The 6- to 9-hour time window analysis suggests that the presence of perfusion/diffusion mismatch as a marker of tissue at risk may be a more important predictor of therapeutic response than duration of symptoms. Furthermore, as in DIAS,¹⁰ there was a strong positive correlation ($P=0.003$) between reperfusion and good clinical outcome, which is consistent with a recent report of patients receiving IV rt-PA, which found that a decrease in the volume of pretreatment mean-transit-time defect by 30% or greater 2 to 3 hours after treatment was a highly significant predictor of clinical recovery.¹²

DIAS and DEDAS provide preliminary evidence that 125 $\mu\text{g}/\text{kg}$ is a safe and effective dose of desmoteplase in patients with perfusion/diffusion mismatch on MRI up to 9 hours from stroke onset. If confirmed in the ongoing DIAS-2 study, the combination of perfusion imaging with IV desmoteplase may change the imaging paradigm in acute stroke and increase the number of potentially treatable patients.

Appendix

The following centers recruited patients to DEDAS (Center, Principal Investigator and number of patients): US-Cleveland, OH: Sila (7), US-Madison, WI: Newman (7), US-Chattanooga, TN: Devlin (6), US-Nashville, TN: Kaminski (3), US-Los Angeles, CA: Starkman (2), US-Louisville, KY: Rimmel (2), D-Leipzig: Schneider (2), US-New

Hyde Park, NY: Libman (1), US-Great Falls, MT: Dietrich (1), US-Stony Brook, NY (1), US-Boston, MA: Selim (1), US-Kansas City, KA: Dafer (1), US-Dallas, TX: Unwin (1), US-Lexington, KY: Pettigrew (1), D-Heidelberg: Hacke and Ringleb (1), D-Ulm: Huber (1).

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IDMC: Kennedy Lees (Chair), Lawrence Wechsler, Rüdiger von Kummer, Walter Lehmacher.

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Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): Evidence of Safety and Efficacy 3 to 9 Hours After Stroke Onset

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