Results of Membrane-Activated Chelator Stroke Intervention Randomized Trial of DP-b99 in Acute Ischemic Stroke

Kennedy R. Lees, MD, FRCP; Natan Bornstein, MD; Hans-Christoph Diener, MD; Philip B. Gorelick, MD; Gilad Rosenberg, MD; Ashfaq Shuaib, MD; for the MACSI Investigators*

Background and Purpose—DP-b99, a lipophilic moderate-affinity chelator of zinc, was postulated to improve recovery after acute ischemic stroke. We evaluated the safety and therapeutic effects of DP-b99 in patients with acute hemispheric ischemic stroke.

Methods—The Membrane-Activated Chelator Stroke Intervention trial was a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial of intravenous DP-b99 administered for 4 consecutive days (NCT00893867). Acute ischemic stroke patients within 9 hours of onset, but untreated by alteplase, with a baseline National Institutes of Health Stroke Scale score of 10 to 16, and evidence of language dysfunction, visual field defect, and neglect were eligible. The primary efficacy analysis compared distributions of functional status measured by modified Rankin score in the intent-to-treat population of patients with any post-treatment outcome, adjusted for initial severity. Functional and neurological recovery were secondary measures. Home time was an exploratory endpoint.

Results—Enrollment terminated at n=446 after the planned interim analysis determined futility; follow-up continued. Final modified Rankin score distributions were equal between DP-b99 and placebo-treated groups (P=0.10; Padj=0.21). Fewer patients recovered to modified Rankin score ≤1 in the DP-b99–treated group (45/218; 20.6%) than after placebo (63/219; 28.8%) (P=0.05; Padj=0.10). Similarly, fewer patients attained National Institutes of Health Stroke Scale ≤1 after DP-b99 (42/218; 19.3%) than placebo (56/219; 25.6%; P=0.10; Padj=0.26). Mortality was similar between DP-b99 and placebo intent-to-treat groups (36/218; 16.5% vs 33/219; 15.1%; P=0.68). Home time was unchanged by treatment (median 36 vs 36.5 days; P=0.25).

Conclusions—Despite encouraging preclinical and phase II trial data, DP-b99 shows no evidence of efficacy in treating human ischemic stroke. (Stroke. 2013;44:XXX-XXX.)

Key Words: acute treatment • neuroprotection • randomized controlled trial

Despite compelling evidence for the therapeutic benefits of acute intervention with intravenous alteplase and possibly with endovascular treatments, many patients with acute ischemic stroke are not able to be offered effective treatment. The effects of stroke may be devastating, with substantial societal and economic consequences. To date, attempts to ameliorate early damage or promote recovery through drugs other than those that target reperfusion have been unsuccessful. However, the importance of the condition militates against abandoning potential treatments without adequate testing.

Loss of ion homeostasis is a feature of acute cerebral ischemia. Zinc, which has both signaling and direct neurotoxic roles, may be implicated in detrimental processes during ischemia. The membrane-activated, zinc-specific chelating agent DP-b99 was postulated to offer neuroprotective or neurorestorative effects in experimental stroke. DP-b99 seemed well tolerated by patients with acute stroke, and a phase IIb trial reported better outcomes among DP-b99–treated patients than a control group on a secondary outcome measure. Post hoc subgroup analysis suggested that the greatest intergroup difference was present among patients with stroke of moderate severity (National Institutes of Health Stroke Scale [NIHSS] 10 to 16) who had features suggestive of cortical damage. The Membrane-Activated Chelator Stroke Intervention (MACSI) trial (NCT00893867) was designed to confirm or refute whether DP-b99 improved outcome after acute ischemic stroke in this selected population. The full background and trial protocol have been described previously.
Methods

Design
MACSI was a randomized, double-blind, placebo-controlled, parallel-group study. For eligibility, patients were to be treated within 9 hours of onset of symptoms of acute ischemic stroke involving ≥1 cortical features (language dysfunction, visual field defect, and neglect). They should have moderate stroke severity as defined by an NIHSS score of 10 to 16. They could not have received treatment with intravenous alteplase or endovascular intervention. Patients or their approved proxy gave informed consent according to a protocol approved by the relevant institutional review boards. Randomization was centrally managed by an interactive voice/web-based randomization system that specified vial numbers to be used for treatment without revealing the contents of any vial to achieve masking of all site personnel and patients. Enrollment was stratified according to time-to-treatment after stroke onset: 0 to 4.5 hours and >4.5 to 9 hours. Investigational treatment was with identical placebo (1.0 mg/kg per day mannitol with 2% polysorbate) versus 1.0 mg/kg per day DP-b99 infused over 2 hours, administered intravenously for 4 days. Each 2-hour infusion was preceded by a 5-minute loading bolus comprising 7% of the dose. Otherwise patients received standard care according to published guidelines.\(^1\)\(^9\)\(^2\)\(^0\)

Safety was evaluated on the basis of treatment-emergent adverse events, physical examination, 12-lead ECG, vital signs, and laboratory tests (complete blood count, chemistry, and urinalysis). A Data and Safety Monitoring Board (DSMB) reviewed safety data periodically and oversaw the interim analysis. This analysis was scheduled to be performed for futility after primary end point data were available from 385 patients (50% of planned enrollment of 770). For administrative reasons and with prior agreement of the steering committee of international stroke experts advised on the trial management, including provision of the interactive voice/web-based randomization system that specified vial numbers to be used for treatment without revealing the contents of any vial to achieve masking of all site personnel and patients. Enrollment was stratified according to time-to-treatment after stroke onset: 0 to 4.5 hours and >4.5 to 9 hours. Investigational treatment was with identical placebo (1.0 mg/kg per day mannitol with 2% polysorbate) versus 1.0 mg/kg per day DP-b99 infused over 2 hours, administered intravenously for 4 days. Each 2-hour infusion was preceded by a 5-minute loading bolus comprising 7% of the dose. Otherwise patients received standard care according to published guidelines.\(^1\)\(^9\)\(^2\)\(^0\)

The primary efficacy outcome was the mRS score at day 90 or at last rating.\(^1\)\(^0\) The score was compared between treatment groups using the Cochran–Mantel–Haenszel test with modified ridit scores (shift, or distribution, analysis).\(^1\)\(^1\)\(^1\)\(^2\)\(^3\)\(^2\)\(^4\)

The sample size of 770 patients was chosen based on Monte Carlo simulations to deliver 80% power to detect efficacy if the true effect of DP-b99 was 70% of the magnitude observed among patients with baseline NIHSS scores of 10 to 16 in the phase Ib study.\(^1\)\(^7\)\(^8\)

Role of the Funding Organization
The sponsor of the MACSI trial was D-Pharm Ltd. An independent steering committee of international stroke experts advised on the design and implementation of the study, received and implemented DSMB recommendations, reviewed all data analyses, and handled all decisions on publication. The principal investigator (K.R.L.) wrote the first draft of the article, supervised secondary analyses, and had access to all study data. Trial management, including provision of the interactive voice- or web-based randomization system, monitoring, data management, and principal statistical analyses, was handled by Cato Research Ltd. Supplementary statistical analyses were undertaken by Rachael Fulton and KRL, University of Glasgow. A sponsor representative (G.R.) attended steering committee meetings in a nonvoting capacity and had an opportunity to review and comment on the final manuscript; Data from the MACSI trial have been lodged with the Virtual International Stroke Trials Archive (VISTA).\(^2\)\(^6\)

Results
Between December 2009 and January 2012, 446 patients were randomized, and 437 had at least 1 postbaseline efficacy measurement (Figure I in the online-only Data Supplement). Their age range ranged from 29 to 85 years, and 95% were white; 224 were men (Table).\(^3\)\(^5\)

Primary Efficacy End Point
The futility analysis based on efficacy end point data from 350 patients estimated conditional power for trial success to be under the prespecified limit of 20%. On recommendation of the DSMB, further enrollment was immediately terminated. Existing patients completed follow-up as planned. Between enrollment closure and completion of follow-up in the remaining 87 patients, the sponsor and steering committee reviewed unblinded group analyses but had no access to individual patient data. The analysis of mRS rank distribution at day 90 (adjusted only for prestroke mRS) in the eventual 437 subjects of the intent-to-treat cohort indicated no difference between the placebo and DP-b99 groups (P=0.105; \(P\) adjusted for baseline age and NIHSS=0.21; Figure 1).

Secondary Efficacy End Points

Recovery on mRS (attainment of mRS ≤1) was lower in the DP-b99-treated group (45/218; 20.6%) than in the placebo-treated group (63/219; 28.8%; unadjusted \(P=0.05\); \(P\) adjusted for baseline age and NIHSS=0.10).

| Table. Baseline Characteristics of the Study Population |
|-------------|-------------|-------------|-------------|
| Overall    | DP-b99     | Placebo    |
| N=437      | n=219      | n=219      |
| Age, y; mean (SD) | 73.0 (9.6) | 69.7 (11.8) | 71.3 (10.9) |
| Subgroup age ≤60 y (%) | 24 (11) | 43 (20) | 67 (15) |
| Subgroup age 61–79 y (%) | 131 (60) | 125 (57) | 256 (59) |
| Subgroup age ≥80 y (%) | 63 (29) | 51 (23) | 114 (26) |
| Sex: men (%) | 114 (52) | 110 (50) | 224 (51.3) |
| NIHSS median (range) | 12.5 (10–16) | 13.0 (10–16) | 13.0 (10–16) |
| Previous stroke (%) | 48 (22) | 38 (17) | 86 (20) |
| Previous TIA (%) | 23 (11) | 20 (9) | 43 (10) |
| Onset to treatment delay hours (SD) | 6.9 (1.7) | 7.1 (1.6) | 7.0 (1.6) |
| Diabetes mellitus (%) | 11 (5) | 13 (6) | 24 (5) |
| Atrial fibrillation (%) | 39 (18) | 32 (15) | 71 (16) |
| Previous myocardial infarction (%) | 11 (5) | 7 (3) | 18 (4) |
| Hypertension (%) | 115 (53) | 102 (47) | 217 (50) |

Demography of the intent-to-treat population (all randomized patients who received any investigational material and had at least 1 post-treatment outcome assessment). NIHSS indicates National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.
Recovery on NIHSS (attainment of NIHSS ≤1) was lower in the DP-b99–treated group (42/218; 19.3%) than in the placebo-treated group (56/219; 25.6%; unadjusted \( P = 0.10; P_{\text{adj}} = 0.26 \)).

Median home time was 36.0 days in the DP-b99 group and 36.5 days after placebo (\( P \) adjusted for baseline age and NIHSS = 0.25). All prespecified outcomes are displayed in Figure 2.

Safety
There was no difference in mortality rates (intent-to-treat population: 36/218, 16.5% and 33/219, 15.1%; \( P = 0.68 \)) for DP-b99 and placebo, respectively (safety population: 37/220, 16.8% vs 33/220, 15%). The rates and nature of serious and non-serious adverse events were similar between groups (Tables I and II in the online-only Data Supplement).

Post Hoc Analyses
No evidence for a biologically plausible beneficial effect was seen in exploratory analyses requested during article review (Figure III in the online-only Data Supplement).

Discussion
The experimental and early clinical background to the MACSI trial with DP-b99 has been discussed elsewhere.\(^\text{18}\) Whether more extensive preclinical studies could have reliably predicted the negative result of MACSI remains an open question that is outside the scope of this article. The mechanism was novel, and the doses used in MACSI exceeded those considered sufficient to penetrate penumbral tissue. In a field with so many failures to demonstrate neuroprotection except by mechanisms that enhance perfusion, the main justification for commencing another large trial was the suggestion of efficacy.
from the previous phase IIb trial. It is acknowledged that this previous evidence consisted of a trial that had been neutral on its primary end point: a change in neurological score. However, change in neurological score has attracted criticism for use as a primary outcome measure in part because it does not reflect an outcome that is functionally important to the patient or society and in part due to statistical disadvantages that arise when interpreting results in patients who die or withdraw. The phase IIb trial had encouraging results based on the currently favored outcome measure of mRS score distribution,23,24 MACSI was designed specifically to confirm or refute findings using this preferred outcome measure. The population was highly selected to mirror a subgroup within the phase IIb trial who had moderately severe cortical ischemia, in whom maximal apparent benefit had been observed and in whom benefits suggested by theoretical considerations could be optimal. This approach strengthens the test of the underlying hypothesis; it does not strengthen the underlying hypothesis.

The MACSI trial excluded patients treated with intravenous alteplase or considered suitable for other reperfusion approaches according to local protocols. The rationale for this and its potential implications are discussed in the protocol.18 This inevitably extended the onset to treatment time and may have contributed to selection of patients with limited reversibility of their ischemic damage. However, it mirrors the selection criteria applied in the phase IIb trial.17 We found no evidence from post hoc exploratory analyses that factors such as delayed treatment or inclusion of patients with previous stroke/symptoms had an appreciable influence on the trial results, although they may contribute to the minor adverse trend. Such trends would be seen in any sample with a frequency of 1 in 5, and the fact that the trial was stopped early for futility inevitably favors reporting of an adverse trend in the final population (because false-positive trends at interim analysis will lead to trial continuation). Furthermore, the baseline age and NIHSS scores slightly favor the control group. The absence of any adverse reaction that could drive a disadvantage, the statistical uncertainty around the estimate, this bias from the futility analysis, and the existing data from the phase II trial all suggest that DP-b-99 has no effect in either direction.

The outcome measures used in MACSI are widely favored as appropriate for acute stroke trials. The analysis was conducted by both ordinal and dichotomized methods, and the results were consistent across each analysis. The combined data from the phase II trial and MACSI are neutral. There is no evidence that DP-b-99 offers any clinical benefit when administered within 9 hours of symptom onset to patients with acute ischemic stroke.

Disclosures
Lees reports fees from PhotoThera, Grifols, Lundbeck, Ferrer, D-Pharm; Bornstein from Dpharm. Diener reports grants from German Research Council, European Union, Heinz-Nixdorf Foundation, German Ministry of Education and Research (BMBF); National Institutes of Health; Bertelsmann Foundation; support from GlaxoSmithKline, Boehringer Ingelheim, Sanofi, Syngis and Talecris; fees from Allergan, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Covidien, Duichti-Sankyo, D-Pharm, EV3, MSD, Medtronic, MindFrame, Neurobiological Technologies, Pfizer, Sanofi, Schering-Plough, Servier, Thrombogenics Gorelick reports grants from Lundbeck and fees from Braingate. Rosenberg is an employee of D-Pharm Ltd. Shuaib reports grants from Bayer, Pfizer, BI, CoAxia, Photothera, AGA Medical, DPharm, Braingate, Asubio, AGA Medical, Cato Research; and fees from AstraZeneca, Bayer, BI, Sanofi, Roche, Pfizer, Merck Frost, BMS, Pfizer, BI, Sanofi, Bayer, Lundbeck, D-Pharm, and CoAxia.

References
Lees et al. MA CSI Randomized Trial


*APPENDIX I

Steering Committee
K.R. Lees (chair), N. Bornstein, H.-C. Diener, P.B. Gorelick, G. Rosenberg (D-Pharm nonvoting representative), A. Shuaib

Data and Safety Monitoring Board (DSMB)
F. Fazekas (chair), I. Ford, J.P. Mohr

Trial Management Team at D-Pharm
G. Rosenberg, L.S. Marshall, P. Geffen

Contract Research Organization (Cato Research Ltd)
A. Bibliowicz, D. Michel, H. Rotmensch, R. Schuckelt

Statisticians (Cato Research Ltd)
D. Ding, T. Soeder

Principal Investigators Contributing to the Study

Population, by Country

Number of patients enrolled in each country is given in parentheses. NC denotes National Coordinator.

Austria (15): A. Gatterer, F. Gruber (NC), J. Willeit, J. Weber
Brazil (13): C.H. Cabral Moro, G. Sampaio Silva, M.S. Rocha (NC), S. Fabio
Canada (4): A. Shuaib (NC), B. Buck
France (14): D. Sablot, F. Rouanet, H. Hosseini, P. Amarenco, T. Moulin
Israel (18): B. Weller, D. Tamne, E. Dorodnicov, N. Bornstein (NC), R. Leker, Y. Lampl
Italy (28): G. Micieli, R. Eleopra, D. Guidetti, E. Bottacchi, G. Agnelli, G. Comi, G. Bono, M. Melis, P. Stanzione, V. Di Lazzaro
Netherlands (2): T. Schreuder
Portugal (24): L. Cunha, T. Pinho Melo, V. Salgado (NC), V. Cruz
Serbia (2): M. Savic
Slovakia (89): G. Krastev, J. Vyletelka, M. Dvorak, M. Brozman, V. Nosal
Switzerland (4): P. Lyrer (NC)
United States (5): A. Vaishnav, C. Pineda, E. Veznedaroglu, S. Mallenbaum
Results of Membrane-Activated Chelator Stroke Intervention Randomized Trial of DP-b99 in Acute Ischemic Stroke

Kennedy R. Lees, Natan Bornstein, Hans-Christoph Diener, Philip B. Gorelick, Gilad Rosenberg, Ashfaq Shuaib and for the MACSI Investigators*

*For correspondence.

http://stroke.ahajournals.org/content/early/2013/02/07/STROKEAHA.111.000013

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/early/2013/02/07/STROKEAHA.111.000013

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/