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Intravenous NPA for the treatment of infarcting myocardium early

InTIME-II, a double-blind comparison of single-bolus lanoteplase vs accelerated alteplase for the treatment of patients with acute myocardial infarction

The InTIME-II Investigators

Aims To compare the efficacy and safety of lanoteplase, a single-bolus thrombolytic drug derived from alteplase tissue plasminogen activator, with the established accelerated alteplase regimen in patients presenting within 6 h of onset of ST elevation acute myocardial infarction.

Methods and Results 15 078 patients were recruited from 855 hospitals worldwide and randomized in a 2:1 ratio to receive either lanoteplase 120 KU . kg^{-1} as a single intravenous bolus, or up to 100 mg accelerated alteplase given over 90 min. The primary end-point was all-cause mortality at 30 days and the hypothesis was that the two treatments would be equivalent. By 30 days, 6·61% of alteplase-treated patients and 6·75% lanoteplase-treated patients had died (relative risk 1·02). Total stroke occurred in 1·53% alteplase- and 1·87% lanoteplase-treated patients (ns); haemorrhagic stroke rates were 0·64% alteplase and 1·12% lanoteplase ($P=0·004$). The net clinical deficit of 30-day death or non-fatal disabling stroke was 7·0% and 7·2%, respectively. By 6 months, 8·8% of alteplase-treated patients and 8·7% of lanoteplase-treated patients had died.

Conclusion Single-bolus weight-adjusted lanoteplase is an effective thrombolytic agent, equivalent to alteplase in terms of its impact on survival and with a comparable risk-benefit profile. The single-bolus regimen should shorten symptoms to treatment times and be especially convenient for emergency department or out-of-hospital administration.
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Key Words: Acute myocardial infarction, bolus lytic therapy, lanoteplase.

See page 1996 for the Editorial comment on this article

Introduction

In thrombolytic-eligible patients with acute myocardial infarction, early complete patency is associated with better left ventricular function and better short-term survival, which is sustained to 1 year and beyond[1–3]. In the GUSTO I trial, the superiority of the accelerated (90 min) alteplase regimen was clearly identified. However, this regimen is cumbersome to administer and so other thrombolytic agents which give rise to comparable patency but which have far simpler administration schedules are worthy of consideration.

Lanoteplase is one such compound. Derived from alteplase (tissue plasminogen activator) by the deletion of the finger and epidermal growth factor domains and the mutation of amino acid Asn-36 to Glu-36, these changes extend the in vivo half-life to 37 min, compared with 4–6 min for alteplase, without affecting efficacy at therapeutic concentrations[4]. The prolonged plasma half-life suggested that a single bolus schedule would be sufficient for therapeutic thrombolysis in acute myocardial infarction. A dose-ranging, phase II, angiographic patency study has shown comparability of a 120 KU . kg^{-1}, lanoteplase bolus with the 90 min alteplase regimen with no increase in bleeding or other complications[5] (InTIME-I Angiographic Study). In order to determine the effect of lanoteplase on survival, these two treatment schedules were then compared in the InTIME-II Trial, where the primary hypothesis was that by 30 days the two treatments would be equivalent with regard to survival.

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Methods

Patient population

Patients eligible for entry into the trial were those greater than 18 years of age who presented within 6 h of the onset of symptoms with at least 30 min of chest pain. Patients were required to have electrocardiographic ischaemic ST segment elevation of equal to or greater than 0·1 mV in any two contiguous limb leads, or equal to or greater than 0·2 mV in any two contiguous chest leads, or equal to or greater than 0·2 mV ST segment elevation in lead V_4R, or equal to or greater than 0·2 mV in two contiguous posterior leads. Patients with new, or presumed new, complete left bundle branch block were eligible also.

Patients were excluded from further consideration if they were pregnant or lactating, had a perceived increased risk of severe bleeding, any history of cerebrovascular accident including previous transient ischaemic attack, a systolic blood pressure of equal to or greater than 180 mmHg or a diastolic blood pressure equal to or greater than 110 mmHg at any time during screening. Blood pressure reduction to below these levels did not make the patient eligible. Additional exclusion criteria were Killip Class 4 on admission, platelet count less than 100 000 cells per mm^3, receipt of more than 7500 units of intravenous heparin in the 2 h preceding potential randomization, use of ReoPro (abciximab) in the 24 h preceding randomization, concomitant use of oral anticoagulants (unless the International Normalised Ratio was known to be less than 2·0), prior involvement in the study, or exposure to any other investigational drug treatment or device within 30 days of presentation. The Ethical Committees of all participating hospitals approved the study and all patients gave informed consent.

Drug regimen and randomization

This was a randomized double-blind study. Treatment was either lanoteplase (Bristol Myers Squibb, Princeton, NJ, U.S.A.) in a dose of 120 KU per kg as a single bolus or the standard 90 min accelerated infusion of alteplase (Genentech, South San Francisco, CA, U.S.A. and Boehringer Ingelheim, Ingelheim, Germany). The treatment allocation for each patient was obtained via the central telephone randomization centre (Nottingham Clinical Trial Data Centre) with allocation in a 2:1 ratio favouring lanoteplase. A double-dummy technique was used to preserve blinding.

Other therapy

Before initiation of study medication all patients without contraindication were given oral aspirin in a dose of 150–325 mg (or intravenous aspirin 150 to 500 mg). Aspirin was then maintained in the range of 100–325 mg once a day thereafter.

Intravenous heparin (70 units per kg to a maximum of 4000 units) as a bolus followed by an infusion of 15 units per kg per hour (to a maximum of 1000 units per hour) was started before or concurrently with the initiation of study medication and then continued for 24–48 h. The maintenance heparin infusion was adjusted to maintain the activated partial thromboplastin time between 50 and 70 s. Initially, it was recommended that the first activated partial thromboplastin time be measured 6 h after the commencement of heparin administration and thereafter according to a supplied nomogram. In May 1998 the Executive Committee for the trial recommended that the first activated partial thromboplastin time measurement should be advanced from 6 h to 3 h in order to permit earlier adjustments of the heparin infusion following the observation that the overall mean activated partial thromboplastin time value at 6 h was higher than expected. Other antianginal therapy, including additional thrombolysis or rescue PTCA, was permitted and could be used according to local practice.

Study end-points

The primary end-point of the study was all-cause mortality to 30 days, but all patients were followed until the last patient had reached 6 months from randomization. Secondary end-points included total stroke, haemorrhagic stroke, all-cause mortality during the first 24 h, net clinical deficit — defined as all-cause mortality or disabling non-fatal stroke — by 30 days and 6 months, in-hospital new onset or worsening heart failure, need for coronary revascularization, and recurrent non-fatal myocardial infarction.

Bleeding episodes were classified according to TIMI criteria (major: causing haemodynamic compromise and requiring surgical intervention or blood transfusion, moderate: requiring blood transfusion or minor: no haemodynamic compromise or need for blood transfusion). It was mandated that all the intra-cranial events be thoroughly investigated and the data reviewed by a blinded stroke evaluation committee.

All ischaemic events following randomization were identified and a pre-defined algorithm was used to determine those events to be classified as re-infarction. Where the algorithm produced a diagnosis which differed from that supplied by the investigator, or where any doubt remained as to the correct diagnosis, the event was reviewed by a blinded critical event committee.

Study management

Patient case record forms were sent to the TIMI Co-ordinating Centre (U.S.A., Canada, Argentina, Brazil, Mexico, Chile, Uruguay) or to the Nottingham Clinical Trial Data Centre (NCTDC) (Europe and South Africa) for initial scrutiny. Thereafter, NCTDC was responsible for data handling and statistical analysis.

Site management and monitoring were conducted by personnel from the Sponsor, Bristol-Myers Squibb, NCTDC and the TIMI Office, together with additional contracted parties. An ongoing programme of source document verification and site audit confirmed that sites had executed their responsibilities to the study to the highest standard.

Day-to-day management of the study was conducted by an Operations Committee, with overall responsibility for direction and conduct resting with an Executive Committee. Committee membership is given in Appendix 1.

Throughout, patients' interests were represented by a Data and Safety Monitoring Board (DSMB). The responsibilities and duties of the DSMB were defined by a charter which was drawn up jointly by the DSMB and the Executive Committee prior to the start of recruitment. Thereafter, the DSMB monitored progress, permitting the trial to continue to its conclusion.

Statistical considerations

Several studies of thrombolytic agents have sought to demonstrate the equivalence of the agents in question with respect to overall mortality rates[6–8]. More recently, the FDA have offered a definition appropriate for the registration of a new thrombolytic agent. As studies vary with respect to the end-point event rate, the FDA have suggested that treatments should be compared using an estimate of the relative risk. A new thrombolytic agent would then be judged to be equivalent to the 90 min regimen of alteplase if the upper limit for the one-sided 95% confidence interval for the relative risk (new agent/alteplase) does not exceed 1·143.

This figure was not available when the InTIME-II trial was being planned and arguments were advanced at that time for a less stringent threshold of 1·196. Assuming that the two treatments had identical mortality rates, a total sample size of 15 000 patients randomized 2:1 in favour of lanoteplase gave the study 90% power to demonstrate equivalence according to the less stringent criterion. As lanoteplase is a new agent, the 2:1 randomization was chosen so that more data was available to assess safety.

Interim analyses were carried out after 25%, 50% and 75% of patients had been recruited. These analyses addressed the question of the superiority of lanoteplase over alteplase with respect to all-cause 30-day mortality alone, with the intention that the study would stop early only if the observed significance level for the test of superiority was less than that specified by the Lan-DeMets rule with the O'Brien-Flemming boundary. In the event, the study proceeded to full recruitment. These analyses have negligible impact on the final test for equivalence for either choice of threshold.

Standard statistical methods appropriate for two group trials were used with confidence intervals for relative risks calculated using Feiller's theorem. Estimates of mortality as a function of time from randomization were obtained using the Kaplan–Meier method. Mean activated partial thromboplastin time values were estimated as a function of time from randomization using a robust smoothing procedure[9].

Table 1 Comparability of treatment groups at randomization

	Lanoteplase n=10 038	Alteplase n=5022
Age (years), median (25%, 75%)	62 (52, 70)	61 (52, 70)
Age ≥75 years (%)	13·8	13·5
Male (%)	75·4	75·1
Current smoker (%)	45	44·9
Systolic BP (mmHg) (mean)	138·69	138·47
Diastolic BP (mmHg) (mean)	82·03	81·99
Heart rate (beats . min^{-1}) (mean)	75·78	75·83
Previous MI (%)	16·3	15·5
Previous angina (%)	21·8	20·1
Previous CABG (%)	2·5	3
Hypertension (%)	30·2	31·0
Diabetes (%)	13·5	14·7
Killip class I (%)	87·2	87·8
ST elevation (%)		
Anterior	42·5	41·2
Inferior	56·6	58·1
Unknown	0·8	0·7
Time between onset of symptoms and treatment (h), median (25%, 75%)	2·83 (2, 4)	2·9 (2·03, 4)

Results

Recruitment

Recruitment commenced in July 1997 and was completed in January 1999. In total, 10 051 patients were randomized to receive lanoteplase and 5027 patients to receive alteplase. Patients were recruited by 855 sites from 35 countries. Some 3291 patients were recruited in North and South America, with the major contribution from Canada (1557) and U.S.A. (1327). The remainder, 11 787 patients, came either from Europe or South Africa with the U.K. (2360), Germany (2334) and Poland (1256) each recruiting in excess of 1000 patients.

The two treatment groups were well matched for demographic and prior morbidity variables (Table 1). Twenty five percent were treated within 2 h of symptom onset, a further 50% between 2 and 4 h, and 22% between 4 and 6 h. Three percent were treated beyond 6 h. Confirmation of an acute myocardial infarction was made in 96% of patients.

Mortality

Vital status at 30 days was available for 99·86% of patients. By this time, 6·61% of the alteplase-treated

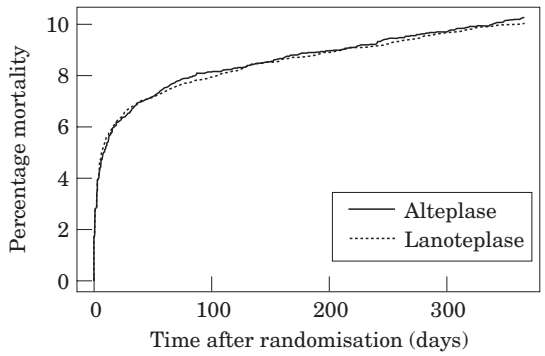

Figure 1 **Kaplan–Meier estimates of mortality for each treatment group at 1 year.**

patients and 6·75% of the lanoteplase-treated patients had died. The relative risk is thus 1·02 and the upper limit of the one-sided 95% confidence interval for the relative risk is 1·137. Vital status was obtained for 98% of patients at 6 months and for 61·5% of patients at 12 months. Figure 1 gives the Kaplan–Meier estimates of mortality for each treatment to 1 year, confirming the similarity of the two treatments in this respect. In the first 24 h following randomization the mortality rates were 2·4%, lanoteplase and 2·5%, alteplase. At 6 months, the Kaplan–Meier estimates are 8·7% and 8·9% for lanoteplase and alteplase, respectively, rising to 10·0% and 10·3% at 1 year.

Strokes

By 30 days, stroke had occurred in 1·87% of patients treated with lanoteplase and 1·53% of those treated with alteplase, $P=0·135$. The large majority of these strokes occurred within the first 48 h of initiation of thrombolytic treatment. Significantly more strokes were adjudicated to be due to haemorrhage in the lanoteplase group as compared with the alteplase-treated patients (1·12% vs 0·64%, $P=0·004$).

Approximately 60% of haemorrhagic strokes led to death prior to day 30. Considering net clinical deficit at day 30 — death or survival with a disabling stroke (defined as a modified Rankin score of 3 or higher) — the event rates were not significantly different; lanoteplase, 7·2% vs alteplase, 7·0%. Residual disability was again assessed at 6 months for survivors of stroke during the index admission. The event rates for net clinical deficit at this time were 8·9% and 9·0% for lanoteplase and alteplase, respectively.

The difference between the treatments with respect to haemorrhagic stroke was unaffected by the protocol amendment to advance the timing of the first activated partial thromboplastin time to 3 h. The incidence was higher in the lanoteplase group both before and after the amendment, lanoteplase, 1·22% vs alteplase, 0·74%, and lanoteplase, 1·0% vs alteplase, 0·51%, respectively.

Cardiac morbidity

Table 2 gives the incidence of reinfarction, heart failure, and the need for revascularization for each of lanoteplase and alteplase for the index admission and out to 30 days. Other cardiac events, not identified as secondary end-points, had similar incidence in each of the groups with the exception of second- or third-degree atrioventricular block (lanoteplase 3·6%, alteplase 4·5%) and acute mitral regurgitation (lanoteplase 0·2%, alteplase 0·4%).

Bleeding events

Excluding intracranial haemorrhage, the incidence of major and moderate bleeding events was very similar to the two treatments; major — 0·5%, lanoteplase vs 0·6%, alteplase; moderate — 2·4%, lanoteplase vs 2·4%, alteplase. However, there were an increased number of minor bleeds in the lanoteplase group (19·7% vs 14·8%, $P<0·0001$).

Concomitant medications

There were no significant differences in heparin use between the two treatment groups. Approximately 17%

Table 2 ***Cardiovascular morbidity subsequent to randomization***

	Lanoteplase (%)	Alteplase (%)	*P*
During index admission			
Severe heart failure	2·3	2·6	0·189
Re-infarction	3·9	4·5	0·073
Need for emergency revascularization	5·4	6·2	0·042
Any revascularization	23·0	24·4	0·053
Severe recurrent ischaemia	16·6	17·7	0·083
To 30 days			
Re-infarction	5·0	5·5	0·142
Need for emergency revascularization	6·3	7·0	0·063
Any revascularization	25·8	26·9	0·148
Severe recurrent ischaemia	19·8	20·7	0·168

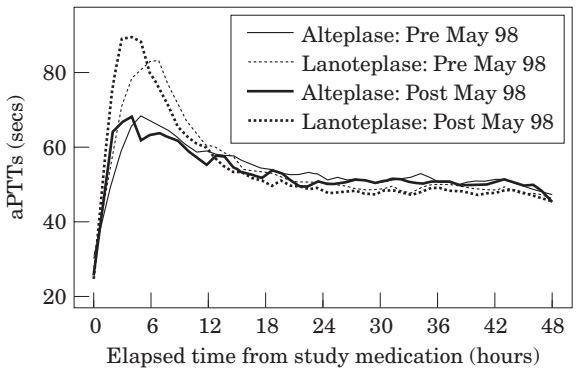

Figure 2 **Activated partial thromboplastin time measurements for lanoteplase and alteplase before and after the May 1998 amendment (see text).**

of patients had received some heparin in the 24 h prior to randomization, 82% received the initial bolus as per protocol and 99% the mandated infusion for a mean duration of 42 h. Some 53% of patients were recorded as receiving heparin beyond that required by the protocol. Of these patients, 72% received intravenous heparin for a further mean 62 h, and 43% received low molecular weight heparin for a mean of 6·7 days.

Figure 2 gives activated partial thromboplastin time values over time for lanoteplase and alteplase both before and after the protocol amendment recommending activated partial thromboplastin time assessment at 3 h. A higher peak level is evident for lanoteplase in both periods, occurring early after initiation of thrombolysis with the profiles being very similar from 12 h onwards.

Use of concomitant aspirin was the same in the two groups with 97% of all patients receiving the initial aspirin dose, 96% continuing with aspirin during index admission and 91% of those patients discharged continuing with aspirin thereafter.

There were no differences between the study groups in the use of other cardiovascular treatments, although their use reflects contemporary practice regarding early initiation of secondary prophylactic measures. ACE inhibitors or angiotensin II antagonists were given to 54% of patients, antiarrhythmics to 16%, oral antiplatelet therapy (other than aspirin) to 14% and intravenous GP IIb/IIIa inhibitors to 3%, intravenous and oral beta-blockers to 20% and 76%, respectively, calcium channel blockers to 13%, cardiac glycoside to 11%, diuretics to 29%, hypolipidaemics to 33%, and oral or intravenous nitrates to 76% and 67%, respectively.

Discussion

The InTIME-II trial has provided clear evidence of the effectiveness of single-bolus weight-adjusted lanoteplase at the 120 KU . kg^{-1} dose. All-cause mortality at 30 days is equivalent to that of alteplase and there is some evidence indicating that coronary ischaemia and the need for subsequent revascularization (PCI or CABG) is reduced relative to alteplase (Table 2). The haemorrhagic stroke rate of lanoteplase was observed to be significantly higher than that for alteplase, but many of the patients suffering cerebral haemorrhage died and the net clinical deficit for the two treatments was almost identical to 6 months. While lanoteplase was associated with a significant increase in the incidence of adverse events involving minor bleeding, there were no differences between the treatments with respect to moderate or major bleeds or the need for transfusion.

The confidence interval obtained for the relative risk of death by day 30 indicates that lanoteplase is equivalent to alteplase both according to the definition of equivalence adopted at the time of study design and according to the more strict FDA definition. The observed 30-day mortality rate for alteplase in this study was 6·61%. The upper limit of the one-sided 95% confidence limit for the relative risk thus translates to an upper limit for the 30-day mortality rate for lanoteplase of 7·52%.

It is now several years since the GUSTO Trial demonstrated a significant reduction in mortality when the 90 min regimen for alteplase was compared with streptokinase, an absolute reduction estimated to be 1·0%. Despite the GUSTO trial, streptokinase remains a common choice of thrombolytic agent throughout cardiology, indicating clearly that any pragmatic definition of clinical equivalence of two thrombolytic agents would allow for a 30-day mortality difference of 1% of more. Against this background, it is clear that InTIME-II has also demonstrated the clinical equivalence of lanoteplase and alteplase.

Lanoteplase is considered to be slightly less fibrin-specific than alteplase and much less than tenecteplase (TNK), which is also administered as a single bolus and which was compared with alteplase in the ASSENT II trial[8], following a very similar study design to that used for InTIME-II. Although both InTIME-II and ASSENT II show the similarity of the respective bolus agents with accelerated alteplase with respect to total mortality and net clinical deficit, there are intriguing differences between the studies with respect to total and haemorrhagic stroke rates. In ASSENT II, the total (and haemorrhagic) stroke rates for tenecteplase and accelerated alteplase were 1·78% (0·93%) and 1·66% (0·94%), respectively. Clearly, there are no apparent differences despite the different fibrin specificity of the two agents. In InTIME-II the same data for lanoteplase and accelerated alteplase were 1·87% (1·12%) and 1·53% (0·62%), respectively.

Stroke, especially haemorrhagic stroke, has emerged as the most significant risk of thrombolytic therapy in acute myocardial infarction[10]. In InTIME-II, the observed haemorrhagic stroke rate of lanoteplase was elevated compared with historical data. It is possible that the dose of 120 KU . kg^{-1} may have been too high, particularly for elderly patients, but since the original placebo-controlled trials[11,12] there has been a general trend across many studies towards higher stroke

rates both overall and for the haemorrhagic subgroup. Although some of this increase may be due to differences between trials with respect to patient demographics, the most likely reason for the trend is the greater acquisition and assessment of diagnostic data to explain both major and minor cerebral pertubations. Viewed against this trend, the haemorrhagic stroke rate for alteplase in ASSENT II is unremarkable, whereas the same rate in InTIME-II is surprisingly low. Clearly, randomized comparisons of treatments within the same trial carry far greater weight than informal inferences from a comparison of data from separate studies. However, stability of effects has been a hallmark of thrombolysis studies and the basis of the widespread use of equivalence trials. The particularly favourable haemorrhagic stroke rate seen for alteplase in InTIME-II remains difficult to interpret and may be, in part, due to random variation.

Aspirin has been a mandatory co-treatment since ISIS-2[13]. Intravenous heparin, especially for tissue plasminogen activators, has been mandated since GUSTO 1, despite the lack of outcome evidence. The heparin protocol in InTIME-II was slightly less intensive than that adopted in previous trials or in the contemporaneous ASSENT II and this is another possible explanation for the observed intra-cranial haemorrhage rates for alteplase. Following the introduction of an early measurement of activated partial thromboplastin time at 3 h, stroke rates were lower in both treatment groups, suggesting that closer monitoring of activated partial thromboplastin time levels may be beneficial. However, the introduction of the 3 h measurement was in response to high stroke rates overall and so the decrease in stroke rates in the latter part of the study contain an element of regression to the mean.

In InTIME-II, the treatment groups were well-balanced with respect to heparin prior to randomization and in the admission of the initial bolus. Figure 2 confirms, therefore, that lanoteplase has a direct effect on activated partial thromboplastin time levels in the hours immediately following administration which differs from that of alteplase. Despite much endeavour in this area, the relationship between thrombolytic agent, the fibrin specificity of that agent, the mode of administration (bolus vs infusion), the concomitant heparin regimen and haemorrhagic stroke incidence is still not resolved. Furthermore, it remains possible that these factors interact with the risk factors for intra-cranial haemorrhage of age, gender and weight.

Following completion of recruitment to InTIME-II, an open registry study of lanoteplase was commenced — InTIME-IIb — which employed an even lower heparin schedule by omitting the initial bolus. These data will be reported shortly.

In conclusion, single-bolus weight-adjusted lanoteplase is an effective thrombolytic agent, equivalent to alteplase in terms of its impact on survival and with a comparable risk-benefit profile. Bolus administration will bring further advantages; ease of administration, reduced time to treatment and a greater potential for administration out of hospital or in the emergency room setting.

This paper is dedicated to the memory of Karl-Ludwig Neuhaus, 1944–2000.

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InTIME-II Appendix

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Argentina (141 patients) — C. Barrero, E. Beck, M. L. Bruno, A. Caccavo, A. Cagide, A. Campo, R. Cermesoni, M. Chahin, O. Dutra, J. Estrada, E. A. Falu, J. Gagliardi, L. E. Garre, A. S. Liprandi, H. Luciardi, B. Mautner, J. Muntaner, G. Nau, S. Salzberg, J. Santopinto, A. Sinisi, H. Torres

Austria (216 patients) — B. Eber, P. Elliott, H. Hiemetsberger, K. Huber, M. Juhasz, P. Kühn, F. Leisch, M. Niktardjam, J. Reisinger, G. Schmalix, R. Schuster, K. Sihorsch, K. Silberhauer, J. Slany, K. Steinbach, K. H. Tragl, A. Valentin

Belgium (287 patients) — K. Al Shwafi, J. Col, P. Dasnoy, M. De Clippel, A. de Meester, H. J. L. P. De Raedt, M. Emonts, P. Evrard, M. Eycken, M. Geboers, G. Heyndrickx, K. Lauwers, K. Mitrie, B. Pirenne, M. Renard, Y. Somers, P. Timmermans, M. Van Kuyk, W. Van Mieghem, J. Vermeulen, J. M. Verrostte

Brazil (115 patients) — D. Albuquerque, J. C. A. Ayoub, A. Carvalho, L. Cesar, O. Gebara, V. Golin, E. Knobel, P. Leaes, J. A. M. Neto, J. C. Nicolau, L. S. Piegas, A. Rabelo Jr., A. Rassi Jr., L. Sila, A. F. Simao

Canada (1559 patients) — T. Ashton, H. Baillie, I. Bata, R. Bhargava, G. Bota, W. Cameron, N. Chan, Y. K. Chan, P. A. Daly, I. Darcel, E. Davies, L. Desjardin, S. Dhingra, J. Ducas, F. L. Ervin, C. Fortin, R. Fowlis, J. Fulop, M. Furey, S. Gagnon, V. Gebhardt, P. Giannaccro, G. Gosselin, J. Graham, F. Grondin, J. W. Heath, M. Henderson, D. R. Hilton, J. Hiscock, W. Hui, L. Kaza, T. Kesselman, P. Klinke, S. Kouz, M. Kucerak, N. LaHoude, M. Lamothe, P. LeBouthillier, J. Lenis, P. Levesque, J. F. Lopez, B. Lubelsky, D. MacRitchie, J.-P.-Mayer, J. D. McDowell, M. Montigny, A. Morris, T. Orestien-Lyall, P. Parekh, K. Pistawka, J. B. Price, G. Pruneau, B. Quinn, B. R. Reid, M. Richmond, B. Rose, R. Schuld, N. K. Sharma, P. Shetty, E. Stanton, H. D. Strauss, B. Sussex, P. Theroux, M. Traboulsi, M. Turabian, C. Turner, S. Vizel, M. Walker, A. Weeks, L. Winkler, G. Zacharias, R. Zimmerman

Chile (61 patients) — J. Bartolucci, P. Castro, M. A. Diaz, G. Illanes, S. Potthoff, E. C. Sanchez, L. M. Silva, J. Yovanovich, F. L. Zanetti

Czech Republic (256 patients) — D. Alan, K. Balázová, P. Boček, J. Cerny, B. Fischerova, M. Holub, J. Hradec, T. Janota, P. Janský, J. Kasper, Z. Klimsa, Z. Motovská, L. Pleva, L. Pluhacek, M. Pšenčka, B. Semrád, J. Spinar, V. Staněk, R. Štípal, P. Suítil, J. Toman, J. Vítovec, D. Wichterie, P. Widimský, K. Zeman

Denmark (21 patients) — C. B. Andersen, P. Grande, J. Kriegbaum, N. Nielsen, P. E. Nielsen, J. B. Schou

Estonia (133 patients) — R. Teesalu, J. Voitk

Finland (93 patients) — H. V. H. Haapamäki, M. Halkosaari, M. Härkönen, S. Jägerholm, P. Kärjä-Koskenkari, P. Karthunen, Y. A. Kesäniemi, H. Koskivirta, P. Lehto, M. Lilja, S. Paakkinen, A. K. Palomäki, K. Pietilä, J. Tuominen, L. Viopio-Pulkki, H. Ylönen

France (684 patients) — I. Adi, P. Admant, A. Akadirik, Z. Alagha, S. Alhabaj, G. Amat, A. A. Andre, F. Apffel, K. Aswad, G. Baradat, P. Bareiss, F. B. Barthers, M. Baudet, M. Baudouy, E. M. Bearez, J. D. Berthou, B. Berzin, G. Bessede, J. J. Blanc, A. Bocara, A. Bonneau, C. Bourdad, J. M. Bouvier, J. Cassagnes, A. Cassat, P. Cazaux, B. Charbonnier, J. Clementy, A. Cohen, D. Coisne, P. Colin, O. Croizier, B. D'Hautefeuille, C. D'Ivernois, P. L. Daumas, C. L. Dauphin, M. F. Deforet, B. Degand, J. L. Dequeker, M. C. Dickele, P. Dugrand, S. Durand, A. Ebagosti, C. Elharrar, O. Equine, E. Fichter, L. Flork, R. Fouche, V. Fourchard, T. Fourme, P. Y. Fournier, F. Funck, D. Galley, E. Garbarz, W. Ghadban, M. Gladin, J. Y. Grall, A. Grand, R. Gryman, N. Guillard, P. Guillo, Y. Haftel, G. Hannebicque, R. Henry, J. F. Huret, L. Janin-Magnificat, J. Jarnier, A. Joly, H. Kamal, A. Khalife, J. L. Roynard, M. Lang, A. Lapeyssonnie, L. Ledain, P. Lejeune, L. Lemetayer, R. Lepori, A. Lombart, J. R. Lusson, O. Magnin, A. Marquand, M. M. Martelet, A. Martelli, C. Mathurin, B. Mentre, D. Messager, M. Morizot, M. J. Mouallem, O. Mouhoub, C. Mycimski, O. Nallet, T. Olive, G. Pacouret, M. C. Palcoux, J. E. Poulard, A. Pruvost, J. C. Quiret, C. Richard, P. Richard, P. Rickaud, V. Riehl-Aleil, A. Rifai, R. Rocher, P. Rotreff, B. Segrestin, M. S. Slama, P. Sultan, X. Tabone, A. Talbodec, M. T. Tissot, C. Toussaint, A. Vahanian, A. Veyrat, Z. Zerrouk

Germany (2336 patients) — M. Adamczak, E. Altmann, B. Altybernd, G. Andreassen, D. Andresen, H. Appenrodt, S. Bachmann, U. Bäcker, U. Beckert, H. M. Behr, W. Beier, T. Beier, D. Berger, R. Bernsmeier, R. D. Beythien, E. Biechl, G. Biedermann, K. O. Bischoff, J. Blerich, H. B. Boch, T. Bonzel, A. R. Both, K. Breidenbach, M. Breuer, H. W. M. Breuer, F. B. Brunkhorst, A. Bruns, H. D. Bundschu, W. Burkhardt, H. J. Busse, K. Caesar, J. Cailloud, A. Chlosta, E. Chorlanopoulos, S. Consemüller, W. Decker, M. Dichgans, R. Dick, K. W. Diederich, C. Dienst, A. Dietz, R. Dißmann, H. Ditter, W. Doering, H. Drost, E. D. Dundalek, D. Eckardt, A. Edelmann, T. Eggeling, G. Eggert, R. Eichner, C. Endres, R. Engberding, H. J. Engel, A. Faehnrich, J. L. Fischer, A. Flor, F. Z. F. Forycki, H. J. Froböse, T. Fruehauf, M. Fuchs, R. Geiser, J. Geletneky, H. Gerdes, B. Gerecke, S. Gesing, H. Gieser, E. Girth, P. Glogner, M. Glover, J. Goetz, H. Goetz, G. Göttfert, M. Gottwik, B. Gregori, M. Grieshaber, C. Großmann, G. Gruber, H. Gunold, W. H. Häßler, B. Hackenjos, O. Hader, H. Hamer, D. Harmjanz, G. Hasst, H. Haun, K. E. Hauptmann, F. J. Hegge, A. Heinze, R. Heinze, K. J. Henrichs, H. Hergenröther, F. Herrmann, C. Herzig, D. Hey, S. Hill, S. Hinzmann, S. Hoffmann, T. Höfs, H. Höhler, G. Holle, B. J. Höltman, T. Horacek, V. Hossmann, F. S. Hübner, C. Hülskamp, R. Hunecke, M. Hust, G. Jaeckh, C. Jebens, E. Jennen, M. Jost, R. Justiz, L. Kallmann, F. Kalscheur, W. Kaschner, W. Kaspar, E. Kauder, B. Keitel, H. Keller, T. Kemkes, N. Kerler, M. Kester, W. Kettner, M. Kilp, A. Kirklies, A. Klaus, H. H. Klein, J. R. Klenböck, H. K. Kley, R. Klingenbeck, H. Koch, B. Kohler, J. Kohler, R. Kolloch, M. Konermann, H. G. Körber, T. K. Kother, V. Kötter, B. Kottwitz, G. Kozariszcsuk, T. Kracht, G. Kratzsch, H. U. Kreft, G. Kreuter, H. Krönert, B. Krönig, E. Krueger, J. Krülls-Münch, H. Kuckuk, M. Kuelschbach, O. W. Kuhrt-Lassay, P. W. Kummerhoff, R. Kunevt, C. U. Kurth, C. Lang, C. Lange, R. Langhoff, A. Laskus, P. Lazarus, H. U. Lehmann, P. Lenga, W. Lengfelder, W. Leupolz, P. Limbourg, U. Loos, W. Lucanus, K. Machill, P. Mäckel, K. G. Mackes, S. Maier, B. Makowski, J. Mandok, M. Manz, W. Mäurer, F. Meier, J. Meier, M. Menges, W. Merx, G. Meurers, U. Michels, C. H. Mickeler, D. Mons, E. Moos, R. Mueller, G. Müller, H. P. Nast, G. Naumann, H. Nebelsieck, J. Neubaur, W. Niederer, J. Nitsch, J. Noack, K. F. W. Nogai, A. Oberheiden, R. Obst, H. R. Ochs, F. Odemar, H. J. B. Odenthal, E. Offers, S. Öhl, H. A. R. M. Ohlmeier, P. Patzer, A. Pech, U. Peters, U. Petry, G. J. Pietschmann, W. Pistner, B. Plappert, W. K. Pohlmann, B. Pollock, H. J. Presser, K. Przytarski, K. L. Puerner, N. Raouf, N. Reike, G. H. Reil, U. Reinhard, V. Riebeling, M. Ritzmann, J. Rödder, E. Roth, R. Rüdelstein, F. Saborowski, B. Sauter, N. Sceffler, A. Schartl, E. Schifferdecker, K. P. Schlotterbeck, J. Schmidt, D. R. Schmidt-Dannert, H. Schmidt-Klewitz, H. J. Schmitz, T. Schnebelt, H. L. Schneider, F. J. Schneider, R. Schoeller, D. Scholz, W. D. Schoppe, G. Schreiner, J. Schroeder, N. Schuh, K. L. Schulte, H. Schulze, H. D. Schulze, P. Schuster, H. P. Schuster, P. Schweizer, U. Sechtem, H. P. Sedlmaier, S. Segel, W. Sehnert, F. Seidel, K. Siedentopf, H. Simon, C. P. Sodomann, C. Solbach, E. Sorges, S. Stabenow, K. P. Stadler, E. Stammwitz, U. Stein, H. Sternberg, C. Stiepak, M. Stockmann, W. Straus, H. Striegel, E. Struch, G. Strupp, T. B. T. Taubert, U. Tebbe, B. Thoeming, A. Thoß, J. Tinnappel, H. Tomsik, H. Topp, S. Troost, A. Überreiter, R. Uebis, T. Ungler, W. Urbaszek, H. F. Vöhringer, T. von Arnim, E. R. von Leitner, A. von Löwis of Menar, H. J. von Mengden, P. von Smekal, W. Voss, P. Wacker, A. Warning, A. Warzecha, U. Wefers, M. Wehr, H. Weigel, F. Weissthanner, P. Weller, M. Werner, A. Wette, H. Wichert, T. Wielage, U. Wiese, T. B. Wilbrand, E. Wilhelms, G. Wilmsmann, F. H. Wolf, T. Wolf, F. C. M. Wonhas, B. Zastrow, U. Zeymer, S. Ziruler, W. Ziss, K. A. Zölch, K. Zwirner

Hungary (427 patients) — D. Becker, M. Bosko, I. Csillag, A. Ermenyi, J. Fogas, K. Heltai, A. Jánosi, A. Katona, C. Kiraly, B. Kiss, G. Kutor, R. Mizik, T. Molnar, M. Mühl, D. Nagy, I. Palacti, L. Rudas, I. Sárosi, K. Simon, E. Sitkel, T. Sydó, F. Szaboki, K. Szikla, T. Szönyi, S. Timar, L. Vándor, K. Zamolyl

Ireland (16 patients) — M. Walsh

Israel (47 patients) — A. Caspi, M. Swissa

Italy (562 patients) — L. Badano, G. Baldacci, E. Balli, D. Banda, G. Baretta, A. Boccalatte, M. L. Borgatti, A. Branzi, C. Burelli, D. Capelletti, A. Capucci, D. Caragiulo, E. Carbonieri, M. Cassin, V. Ceci, M. Cocchieri, C. Coletta, E. Conte, G. M. Contini, G. Corsini, E. D'Annunzio, M. De Blasi, I. De Luca, F. Delciterna, G. Di Pasquale, G. Diguardo, L. Fattore, G. Ferraiuulo, A. Finardi, P. M. Fioretti, G. Giunta, U. Guiducci, G. Guzzardi, G. Horando, G. Ignone, A. Lazzaroli, D. Levantesi, R. Liberati, E. Losi, F. Macor, S. Mangiameli, C. Martines, F. Meinardi, T. Morgera, L. Morozzi, M. Mostacci, F. F. Naccarella, F. Ottani, A. Palamara, A. Pani, L. Paperini, R. Pes, A. Pesola, A. Porzio, A. Raviele, S. Ricci, A. Rosi, R. Rossi, D. Rotiroti, L. Rusconi, G. Sabino, V. Saccone, A. Sanna, G. Scaramuzzino, G. P. Scorcu, F. Semprini, D. Severini, D. Staniscia, L. Tantalo, F. Tartagni, P. Terrosu, S. Tondelli, R. Trichero, E. Uslenghi, S. F. Vajola, A. Vetrano, E. Violi, P. Zardini, G. L. Zingarini, G. Zobbi, G. Zuin

Latvia (36 patients) — U. Kalnins

Lithuania (42 patients) — A. Cârvekülg, J. Laanoca, J. Iacis, L. Lankiene, A. Laucevicius, A. Lukoseviciute, R. Palsauskaite, B. Petrauskiene, W. Soopóld, H. Uuetoa, J. Vilks, R. Vitonyte, I. Zakke

Mexico (83 patients) — J. Dorantes, H. Hernández, C. Jerjes, J. L. Leva Garza, C. Martinez

Netherlands (935 patients) — A. Anneveldt, H. F. Baars, S. C. Baldew, P. E. F. Bendermacher, L. V. A. Boersma, R. J. Bos, R. W. Breedveld, P. W. F. Bruggink, R. Ciampricotti, J. I. Darmanata, A. E. de Porto, G. J. de Weerd, J. W. Deckers, M. P. Freericks, F. A. Hillebrand, J. P. Kerker, J. C. Koenen, M. G. M. Kofflard, K. L. Liem, A. H. Liem, G. C. M. Linssen, R. J. Lionarons, J. R. M. Peters, J. P. Posma, E. W. M. Saat, L. H. Savalle, W. C. G. Smits, M. J. Suttorp, A. C. Tans, R. P. Th. Troquay, G. J. van Beek, A. J. van Boven, R. Van der Heijden, A. Van Hessen, R. A. M. van Langeveld, T. A. R. van Lier, L. W. H. van Loo, J. van Wijngaarden, L. G. P. M. van Ziejl, M. J. Veerhoek, F. Vermer, H. A. Werner

Norway (81 patients) — T. Graven, B. Klykken, O. Meyerdieks, T. M. Omland, J. E. Otterstad, T. Pedersen, R. Rød

Poland (1256 patients) — M. Banaszewski, Z. Bednarkiewicz, G. Bojarski, L. Ceremuzyński, E. Czestochowska, M. Gajewski, M. Galewicz, J. Gorski, Z. S. Grabczewska, M. Gruchaka, K. Janicki, M. Janion, K. Jaworska, M. Jezewska, J. Kakol, M. Kizciuk, A. Kleinrok, P. Kolodziej, P. Komorowski, A. Konopka, J. Kopaczewski, J. Korecki, Z. Kornacewicz-Jach, M. Kowalewski, D. Kratochwil, J. Krolczyk, M. Krzminska-Pakula, P. Kurek, M. Kurowski, M. Kurpesa, J. Kurzawski, R. Kwiecien, L. Lenartowski, M. Lewandowski, K. Loboz-Grudzień, G. Luczak, A. Maliński, M. Michalski, W. Musial, E. Nartowicz, A. Nowicka, A. Odyniec, S. Pasyk, W. Prastowski, A. Przybylski, A. Raczynska, J. Rodzik, M. Romanowski, A. Rynkiewicz, M. Rzyman, Z. Sadowski, A. Sidorowicz, M. Sledziona, W. Sobiczewski, B. Sobkowicz, J. Sobolewska, L. Sokalski, J. Stepinska, M. Sterlinski, M. Stopinski, G. Świątecka, T. Szajewski, Z. Szpernal, H. Tarnowska, E. Trzos, M. Ujda, M. Wierzchowiecki, T. Wodynska, D. Wojciechowski, K. Wrabec, K. Wrzesinski, P. Zuk

Portugal (48 patients) — A. Albuquergue, M. Carrageta, A. Costa, D. Cunha, D. Ferreira, R. Ferreira, J. M. Gaog Leiria, A. Pimenta, E. Rufino, J. Vasconcelos

Romania (35 patients) — M. Aldica, E. Apetrei, S. Balanescu, I. V. Bruckner, R. Capalneanu, N. Florescu, C. S. Georgescu, L. Cherasim, C. Ginshina, A. Merenta, O. Parvu, S. Radutiu, I. Savulescu, I. Vita

Russia (360 patients) — O. Averkov, I. N. Bokarev, N. Gratsiansky, Y. Grigoriev, A. Gruzdev, I. Kakhnovsky, T. V. Kheevehuk, O. Khrustalev, Y. Kobalava, T. B. Konoratieva, V. Koukline, S. Martiouchov, E. Pavlikova, I. Poskotinov, K. Rogalev, M. Ruda, A. Sinopainikov, A. Syrkin, S. T. Tereschenko, I. Yavelov, S. Zavolghin

Slovakia (80 patients) — E. Čurilla, R. Kohn, F. Kovář, J. Murín, P. Poliačik

Slovenia (74 patients) — I. Drinovec, M. Horvat, B. Krivec, J. Markež, R. Pareznik, Z. Pehnec, J. Resman, F. Sifrer, R. Skale, D. Trinkaus, G. Voga

South Africa (569 patients) — M. M. E. Baig, P. Blomerus, B. P. Botha, L. Burgess, A. Dalby, D. Duncan, D. I. Duncan, D. Gillmer, N. Govender, R. J. Jardine, A. Kok, P. Manga, R. K. Naidu, M. C. Rajput, N. Ranjith, J. S. Roos, F. A. Snyders, L. Steingo, A. Stern, F. Z. Tayob, S. Vythilingum

Spain (404 patients) — N. Alonso-Orcajo, A. Arribas Jimenez, J. I. Ayestaran, B. B. G. Balsera, C. Barras, A. Castro, N. Cobo, A. Duque, M. J. Garcia, P. Goiriena, M. Gonzalez-Valdayo, J. M. Gulias Lopez, P. Jimenez Gomez, V. Lopez Garanda, J. López-Sendón, F. Martín Santos, R. Nogueira, P. Pabon Osuna, E. Ponce De Leon, A. Quesada Dorador, R. Paya Serrano, L. Rodriguez, M. Rodriguez, F. Rubio, R. Ruiz-Salmeron, J. Solar, J. Toquero, J. Velasco, V. Vilar Herrero, M. Vizcaino, X. Wancisidor

Sweden (174 patients) — E. Basilier, V. Birgersdotter, E. Björnsdotter, A. Bjurman, D. Hagström, I. Hallin, O. Hansen, L. O. Hemmingson, L. Lundkvist, M. Lycksell, B. Möller, P. Nolgard, G. Sjölund, A. Stjerna

Switzerland (64 patients) — W. Angehrn, E. de Benedetti, M. Diethelm, A. Gallino, G. Plebani, H. P. Vögelin, W. Wojtyna

Turkey (198 patients) — H. Akgöz, G. Akgün, O. Akyürek, M. K. Batur, S. Bayata, N. Deger, O. Emel, C. Gürgün, M. E. Korkmaz, O. Kozan, D. Kumbasar, H. Muderrisoglu, Y. Nisanci, A. Oto, B. Ozin, O. Ozsaruhan, S. Payzin, N. Postaci, H. Sozcuer, B. Tamci, F. Topuzoglu, C. Türkoglu, E. Tutar, M. Ulucam, T. Ulusoy, B. Umman, S. Yalçinkaya, M. Yesil, M. Zoghi

United Kingdom (2363 patients) — P. C. Adams, S. Ahir, A. J. Ahsan, J. Akhtar, C. J. Albers, M. N. Al-Khafaji, N. Anderson, R. J. Bailey, R. J. I. Bain, A. Basu, A. Beal, R. M. Boyle, N. Brown, S. Campbell, D. Card, S. J. Cross, P. Davies, E. T. L. Davis, J. W. Dean, A. Deaner, M. A. Devine, J. Dhawan, J. C. Doig, S. Dubrey, P. G. Dunn, J. Dwight, R. Ecob, H. Fitzpatrick, S. Fletcher, C. M. Francis, A. H. Gershlick, P. E. Glennon, N. E. Goodfield, W. J. Grabau, M. Gray, K. E. Gray, J. Heath, W. G. Hendry, J. Highland, K. Hogg, J. B. Irving, M. A. James, K. Jennings, M. Joy, H. H. Kadr, S. Kahn, P. J. Keeling, P. M. Keir, T. M. Kemp, J. Kinaird, C. Kinsey, K. Knowles, J. S. Kooner, A. Lahiri, C. Lawson, R. Lewis, A. F. N. Macdermott, A. MacKay, D. C. MacLeod, A. J. McCance, A. Morrison, M. Mortimer, D. Mulvey, J. J. Murphy, S. Murray, R. Muthusamy, A. Myers, V. G. Nicolson, D. Northridge, S. Odemuyiwa, K. G. Oldroyd, R. M. Oliver, A. C. H. Pell, J. E. F. Pohl, B. Price, N. Quereshi, A. P. Rae, S. Reader, D. S. Reid, G. W. Reynolds, A. Robinson, R. H. Robson, J. C. Rodger, E. Rodrigues, E. L. Rose, D. B. Rowlands, J. M. Rowley, A. Rozkovec, J. Shreeve, P. Siklos, R. H. Smith, J. F. Sneddon, U. Somasundram, I. Squire, J. D. Stephens, A. Stephens-Lloyd, J. M. Strand, J. Stuart, N. Sutaria, J. Swan, G. W. Tait, R. D. Thomas, M. A. Thompson, G. Tildesley, C. M. Travill, J. A. Treadgold, J. M. S. Trelawney, D. Turner, B. D. Vallance, D. Wallbridge, P. L. Weissberg, E. White, M. Wicks, R. G. Wilcox, P. Wilkinson, J. E. Wiltshire, A. Wright

United States (1339 patients) — B. Andrea, K. Attassi, R. Bahr, J. Banas, K. Baran, M. Belknap, M. Bensman, B. Bertolet, D. Besley, V. Bethala, R. Betzu, R. Bhalla, M. Bhargava, A. Binder, R. Birkhead, K. Bodine, D. Brewer, S. Carey, M. Chengot, J. Coppola, D. Cragg, B. D'Arcy, D. M. Denny, P. DiLorenzo, E. Dixon, A. Doorey, J. Dorantes, D. Doty, W. Doty, M. Drossner, P. Eisenberg, T. Falco, R. Feldman, I. Freman, M. Frey, J. Garcia, J. Glassman, S. Goldman, M. Gomez, M. Gonzalez, P. Goodfield, S. Gottlieb, D. Grech, R. Greene, T. Hack, T. Haffey, J. Hanson, E. Havranek, T. Henry, P. Hermany, H. Hernandez, R. Herron, W. Hession, J. Hines, J. Hochman, R. Hundley, W. C. Jacobs, C. Jerjes-Sanchez, S. Jerome, R. Josephson, J. Kalan, D. Kawalsky, A. Khan, K. Kmetzo, M. Kraemer, E. Lader, J. Landis, J. Lash, R. Leber, W. Leimbach, J.-L. Leiva Garza, W. Maddox, R. Magorien, S. Mahapatra, I. Mantecon, C. Martinez, G. McKendall, R. Mendelson, J. Miklin, J. Milas, R. Miller, B. Molk, E. S. Monrad, P. Moore, J. Morrison, H. Morse, H. Mueller, M. Neustel, D. Nichols, A. Niederman, T. Nygaard, R. O'Connor, W. O'Riordan, S. Obermueller, S. Palmeri, R. Patel, T. Paul, T. Phiambolis, R. Piana, B. Polansky, W. Polinski, G. Ponce, P. Ribeiro, E. Roccario, C. P. Rogers, W. Rogers, A. Rosenblatt, J. P. Runyon, F. Scheel, P. Schmidt, R. Schneider, H. Schwartz, M. Schweiger, R. Shannon, L. Shelhamer, F. Sheridan, W. Shine, T. Shook, S. Siskind, R. Slama, E. Spear, R. Steingart, G. Stouffer, B. Strunk, U. Thadani, G. Timmis, R. Trautloff, A. Tse, B. Wohl, H. Zarren, R. Zucker

Uruguay (7 patients) — F. Kuster, J. P. Pardie