Trends-in-Medicine

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by Lynne Peterson

SUMMARY

AstraZeneca/Renovis's Cerovive is the first neuroprotective to show a positive benefit in a Phase III trial, but the effect is modest, and price may limit usage. However, it does appear to make t-PA safer to administer. The results need to be replicated in the ongoing SAINT-2 trial. ♦ The Phase II data look promising for Paion/Forest's desmoteplase in ischemic stroke, and it is now moving into Phase III. ♦ Novo Nordisk's NovoSeven (rFactor VIIa) looks promising for intracerebral hemorrhage. ♦ Bayer's repinotan failed to show clinical benefit, and development has been discontinued. ♦ Development in acute ischemic stroke is continuing for two generic agents: diazepam and magnesium. ♦ Ferrer still has confidence that citicoline will prove beneficial and is beginning a large trial, ICTUS, with results expected in 2008.

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EUROPEAN STROKE CONFERENCE (ESC)

Bologna, Italy
May 27-28, 2005

The key drug of interest at this meeting was AstraZeneca/Renovis's Cerovive (NXY-059), with the presentation of the first Phase III trial data on this agent. However, there also were data presented or discussed at the meeting on several other neuroprotectants in development.

In most developed countries, about 0.2% of the population suffer a stroke annually (that includes 700,000 Americans and 200,000 Germans), with 66%-80% surviving, and from a third to a half of these becoming permanently disabled. About 88% of strokes are ischemic, and 12% are hemorrhagic.

Hemorrhagic stroke has a mortality rate of ~40%, and half of these deaths occur in the first two days. About two-thirds of those who survive are permanently disabled.

Thrombolysis with intravenous recombinant tissue plasminogen activator (IV r-t-PA) within three hours is the established therapy for ischemic stroke, but very few patients – an estimated 2%-6% – are treated within the three-hour t-PA window of efficacy/safety. The percentage of patients reaching a hospital within the three-hour window also varies widely by country. For example, a pharma source estimated that few patients in the U.K. or Denmark make the three-hour window, but 40%-50% of German patients and a reasonable percentage of French patients do. There are similar geographic variations within the U.S.

A study of 880 stroke patients at 35 centers in five European countries found:

- 19.2% were treated in <3 hours.
- 42.2% were treated from 3-6 hours after onset of symptoms.
- 38.6% were not treated until 6-12 hours after onset of symptoms.

Sources estimated that 33%-50% of patients reach the hospital within six hours of the onset of their stroke. Before a doctor can prescribe t-PA, patients must have a CT scan to rule out a hemorrhagic stroke, but if a CT scan were not required, >50% of stroke patients could be treated within six hours. Even if patients get to the hospital quickly enough, many are not seen by a stroke unit/team, and an expert estimated that death and disability could be reduced 25% just by getting patients to a stroke unit.

Numerous companies have tested neuroprotective agents in stroke, and many of them looked very promising in animals but failed in human clinical trials. Most recently, Merck/Ono's ONO-2506 (arundic acid) failed.

Neuroprotectants Tested in the Treatment of Stroke

Company	Drug	Type	Trial results	Status
---	Magnesium	---	No efficacy	FAST-MAG trial ongoing, sponsored by NIH
AstraZeneca	Zendra (clomethiazole)	γ-aminobutyric acid agonist	No efficacy	Discontinued
AstraZeneca/Renovis	Cerovive (NXY-059)	Free radical scavenger	Modest efficacy; very safe in first Phase III trial	Second Phase III trial, SAINT-2, ongoing
Bayer	Nimotop (nimodipine)	Calcium channel blocker	No efficacy	Discontinued
Bayer	Repinotan	Serotonin agonist	No efficacy	Discontinued
Boehringer Ingelheim	Enlimomab	Anti-intercellular adhesion molecule antibody	Excess risk	Discontinued
Bristol-Myers Squibb	BMS-204352	Potassium channel modulator	No efficacy	Discontinued
Ciba-Geigy	Selfotel (CGS-19755)	NMDA antagonist	Excess mortality	Discontinued
CNSI	Cerestat (aptiganel)	NMDA antagonist	Risks outweighed benefits	Discontinued
Daiichi	Harmokisane (ebselen, PZ-51)	Free radical scavenger	---	Phase III trial ongoing
Ferrer	Citicoline	Membrane stabilizer	Animal and Phase II studies positive, with no safety signal	Pre-IND meeting with FDA expected in August 2005. Phase III ICTUS trial to start in September or October 2005
GlaxoSmithKline	Gavestinel (GV-150526)	Glycine receptor antagonist	No efficacy	Discontinued
Hoffmann-La Roche	Dextrorphan	NMDA antagonist	Caused hallucinations, agitation, and hypotension	Discontinued
Ivax	Cervene (nalmefene)	Narcotic receptor antagonist	No efficacy in Phase III	Discontinued
Johnson & Johnson	Lubeluzole	Nitric oxide modulator	No efficacy	Discontinued
Merck/Ono Pharmaceutical Co.	ONO-2506	Believed to modulate the function of brain astrocytes	Arterial thrombosis events at higher dose, but lower dose less than ideal	Phase II trial failed; outlook now uncertain
Mitsubishi Pharma	Radicut (edavarone)	Free radical scavenger	Effective but risk of liver failure; described as "very similar to Cerovive"	Approved in Japan in 2001; not enough data for the U.S.
Novo Nordisk	Factor VIIa	Human coagulant factor	No major safety concerns in a Phase II safety and feasibility study	FDA approved in hemophilia. Phase III FAST trial began in May 2005
Paion/Forest	Desmoteplase	Anticoagulant from vampire bat enzyme	Phase II studies showed efficacy at 125 μg/kg dose but discordant on 90 μg/kg dose	Phase III DIAS-2 trial to start in summer 2005
Pharmacia & Upjohn	Tirilazad	Free radical scavenger	No efficacy	Discontinued
Yamanouchi	N/A	α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid antagonist	No efficacy	Discontinued

ASTRAZENECA/RENOVIS'S Cerovive (NXY-059)

Cerovive, which works by trapping free radicals, is the first neuroprotective to show positive efficacy results. In the SAINT-1 trial, safety was extraordinarily good, but the efficacy benefit was small, and sources suggested usage may be highly influenced by pricing.

SAINT-1 is the first of two Phase III trials. SAINT-1 and SAINT-2 have identical designs; both are randomized, placebo-controlled, double-blind trials. SAINT-1 was conducted in 24 countries in Europe, Asia, Australia, and South Africa. SAINT-2 is a North American trial.

Patients in both trials got/get a loading dose of 1820 µg Cerovive over one hour, followed by 844 µg/hour Cerovive for 71 hours. Modified Rankin score (mRS) was measured on Days 30, 60, and 90. Patients were allowed to get t-PA, so there was "forced allocation" to ensure the two arms in the trial were evenly matched, and they were. The number of patients in the trial was:

- 1,772 randomized.
- 1,705 measured for safety.
- 1,699 used for ITT analysis.
- 1,525 in the per protocol analysis.

The principal investigator, Dr. Kennedy Lees of Glasgow, concluded, "We have a very high quality trial. Cerovive appears entirely safe. It met the primary efficacy endpoint, was neutral on NIHSS, and showed a positive trend on the Barthel Index (BI)...ICH after thrombolysis was not increased and may be decreased…These are very encouraging and intriguing results, but we need to see the SAINT-2 trial results, which will be available next year at the earliest."

Primary endpoint

The primary endpoint, a shift in mRS (a functional outcome) was met with a p-value of .038. This was used instead of the proportion of patients in mRS 0/1, which has been used in most other neuroprotective trials. The

Other SAINT-1 Trial Results

Measurement	Placebo n=847	Cerovive n=858	p-value
Demographics			
Age	69.5	69.4	---
Men	56.7%	55.4%	---
Time to treatment	105 mins.	227 mins.	---
t-PA use	29.4%	28.0%	---
Hypertension	69.1%	68.9%	---
AF	31.9%	28.0%	---
Prior use of antiplatelets	32.2%	29.0%	---
Results			
Baseline NIHSS	12.5	12.6	---
NIHSS at 3 months	10.8	10.8	---
Secondary endpoint #1: Change in NIHSS at 3 months	-1.7	-1.7	0.864
Secondary endpoint #2: BI≥95	Odds ratio 1.16		0.182
Safety			
Patients with adverse events	670	662	Nss
Patients with serious adverse events	313	296	Nss
ICH after thrombolysis (with t-PA)			
Number of patients	249	240	---
Overall ICH	27.3%	15.4%	<.005
Asymptomatic ICH	20.9%	12.9%	N/A
Symptomatic ICH	6.4%	2.5%	<.05

Additional Analysis of SAINT-1 Results *(calculated, not presented)*

Drug/ Measurement	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5/6 (death)
Placebo	11.0	20.0	11.7	12.7	20.6	24.0
Cerovive	15.4	18.0	11.4	14.2	16.9	24.0
Cerovive vs. placebo	+4.4	-2.0	-0.3	+1.5	-3.7	0
Placebo	42.7			57.3		
Cerovive	44.8			55.1		
Cerovive vs. placebo	+2.1			-2.2		

SAINT-1 Trial Results

Drug	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5/6 (death)	Odds ratio
ITT Analysis							
Placebo	11.0	20.0	11.7	12.7	20.6	24.0	---
Cerovive	15.4	18.0	11.4	14.2	16.9	24.0	1.2 (p=.038)
Shift in mRS (by ITT)	+ 2.4 *		+ 1.2 *		- 3.7 *		---
Per Protocol Analysis							
Placebo	10.5	20.3	12.2	12.5	20.8	23.7	---
Cerovive	15.4	18.5	11.5	14.6	17.6	22.4	---
Shift in mRS per protocol	+3.1		+1.4		-4.5		(p=.028)

*** An AstraZeneca official said the p-values for these shifts have not been released yet.**

SAINT-1 Subgroup Interactions with Primary Endpoint

Measurement	p-value
Treatment-time	0.92
Treatment-age	0.62
Treatment-severity	0.72
Treatment-alteplase (t-PA)	0.93
Treatment-diabetes	0.98
Treatment-glucose	0.27

principal investigator, Dr. Kennedy Lees of Glasgow said no baseline mRS was measured, but in order to enter SAINT-1, patients had to have been mRS 0 or 1 before their stroke.

The FDA reportedly is interested primarily in the results of mRS, not the other endpoints in the trial. Renovis officials have reportedly claimed that the FDA requested the shift in mRS as an endpoint, but that has not been confirmed, and the use of shift in mRS could pose a regulatory hurdle simply because it is a new approach.

Experts find this approach interesting, but some emphasized that this is a new concept and is not validated yet. One commented, "The only reason mRS 0/1 has been used is that it seemed, until now, more consistent." Another expert said, "This is the first trial ever to use shift in mRS. I don't know it. I need to see the (Cerovive) data." A German doctor said, "This is a new way to look at mRS, and it is better than a median. Measuring the shift is a reasonable way to look at it."

Secondary endpoints

- **NIH Stroke Scale (NIHSS)**, a neurological outcome. SAINT-1 missed statistical significance on this endpoint. Dr. Lees called this "disappointing." In a post hoc analysis of responders, the analysis favored Cerovive over placebo.

  Reportedly, European regulators asked for this endpoint, but I believe SAINT-1 and SAINT-2 can be pooled to meet this requirement, and it may be possible for the pooled analysis to be statistically significant even if both SAINT trials individually are not statistically positive. But the pooled analysis must be positive.

- **Barthel Index (BI).** Dr. Lees noted that this endpoint also was missed (not statistically significant), but he said the "trend is in the right direction."

- **Stroke Impact Scale.**

- **EuroQOL.**

Safety

The Kaplan-Meier survival curves were identical. Dr. Lees described the safety data as "the easiest," saying there was "no difference (from placebo). They are virtually the same…There were no adverse events that unblinded the trial. The two arms were very similar, and there was nothing of note. Cerovive was a very well-tolerated and safe drug." However, Dr. Lees said the side effect to watch is any effect on the kidneys, though he said there has been no signal of a problem with that so far.

Points Dr. Lees made about the SAINT-1 trial included:

- No subgroup showed a statistically significant difference on the primary endpoint.
- Cerovive is the first drug to meet all the STAIR criteria for a neuroprotectant, which include:
  - Efficacy in rodents and primates in both transient and permanent models of acute ischemic stroke.
  - Reducing infarct size and preserving brain function.
- Cerovive is well-tolerated in humans. The target plasma concentration of 260 μg exceeds the effective levels (150 μg) in animal models.

Physician reaction to SAINT-1 results

Among the comments stroke doctors had about the findings were:

- *Austria:* "The modified Rankin scale is very important, but it is a very gross scale. It is good for large trials, but a patient with an mRS of 2 is quite dependent. mRS is not usually measured as a shift; it is an outcome measure at a given time point."
- *Norway:* "If it is really safe, then a shift of 2.4% is enough."
- *Germany:* "It doesn't look like much (efficacy), but it is an effect. Compared to the 14% benefit you get with t-PA or the ~30% benefit in the DIAS trial (of Ferrer's citicoline), it is low, but it is the first neuroprotective to show an effect. Many people, including me, warned the company not to expect an efficacy greater than 4%-5%. The company may be disappointed, but 2.4% may have value. It means the number needed to treat is 33, but with a completely safe drug, it will be used. There are definitely more patients who are seen between 3 and 6 hours who could get it, and you can give it with t-PA <3 hours…The benefit is small but measurable, and it is clinically relevant – but no one would pay 2,000 euros per treatment for it."
- *United States (Cerovive investigator):* "The efficacy results are ho-hum…For a neuroprotective, we would expect a 5% benefit…It's better than nothing, but what if all the benefit is in the t-PA-treated subgroup? What if all it does is make t-PA safer by lowering the bleeding rate? But if it could make t-PA twice as safe, that would be big …In the test tube there was some evidence NXY-059 may interact with t-PA levels…We need to know if it halves the t-PA bleeding rate. Then, it would be part of a mandatory cocktail. But it is unclear from this data if patients benefit in isolation (monotherapy)."

Miscellaneous

Other points that may help understand the SAINT-1 results and/or put them in perspective include:

- The SAINT-2 trial must be positive to support SAINT-1, and the CHANT trial also needs to be positive if Cerovive is to be used broadly.

- Asked about the interaction with t-PA, an AstraZeneca official said the covariation for interaction with t-PA was >0.9, which is not statistically significant. He insisted the company wants to establish Cerovive as a therapy in its own right, not in combination with t-PA, "Cerovive has an important effect that needs to be confirmed – that it can treat patients independently of t-PA." Thus, he said, no further details on the t-PA subgroup will be presented.
- No additional data presentations are planned until publication of the data.
- Dr. Lees reportedly wanted to do a Phase IIb trial before SAINT-1, but a source said AstraZeneca wouldn't let him.
- Renovis officials claimed that no subgroup drove the outcome of SAINT-1, and there were benefits across all subgroups.
- Physicians and staff were given training by AstraZeneca on measuring mRS before/during the trial.
- t-PA cuts deaths/disability by 14%, that means that for every seven stroke patients treated with t-PA, one death/dependency is avoided, but only about 2% of stroke patients get t-PA.
- Dr. Lees commented, "It (SAINT-1) was a trial that was not particularly selective (on entry)."
- A neuroprotective drug very similar to Cerovive, Mitsubishi's Radicut (edavarone), is approved in Japan. Apparently, there are not enough data for a U.S. filing on this yet.

90-Day mRECT Trial Results

Measurement	Repinotan n=127	Placebo n=143	p-value
Number of patients by ITT	342	337	---
Number of patients per protocol	292	284	---
Average time to start of drug therapy	3.7 hours	3.68 hours	---
Received t-PA	61%	60%	Nss
Baseline NIHSS	14.7	14.7	Nss
Primary endpoint: Barthel Index ≥85	37.1%	42.4%	0.149
Subgroup analysis: Barthel Index responders			
Patients who got t-PA	40%	47%	---
Patients who did not get t-PA	33%	35%	---
Safety			
Died	20.7%	19.9%	Nss
Any adverse event	98%	97%	Nss
Any drug-related adverse event	21%	22%	---
Any serious adverse event	43.4%	40.4%	---
Discontinuations due to adverse events	10%	7%	---
Cerebrovascular accidents	6%	5%	---
Cerebral hemorrhage	2%	3%	---
Pneumonia aspiration	4%	2%	---
Secondary endpoints			
mRS 0-1-2	32.2%	37.1%	0.169
NIHSS ≥4 improvement	66.7%	69.6%	0.413

OTHER DRUGS/DEVICES IN DEVELOPMENT FOR STROKE

BAYER'S repinotan

This neuroprotectant, a serotonin 5HT1A receptor agonist, failed to show clinical benefit in a Phase IIb trial, and development has been discontinued. Data were presented at the meeting from the three-month, 681-patient, randomized, double-blind, placebo-controlled, parallel-group, multicenter mRECT trial of intravenous repinotan in acute ischemic stroke (given <5 hours from onset). This trial started as a Phase III study but the protocol was changed to a Phase IIb study. Repinotan had to be initiated within 4.5 hours from the onset of ischemic symptoms, and it was infused at a rate of 0.104 mg/hour for two hours, followed by 0.052 mg/hour for 70 hours. Repinotan missed its primary endpoint and the two key secondary endpoints.

CONCENTRIC MEDICAL'S MERCI Retriever

The Retriever embolectomy system uses a coil delivered by catheter to catch a clot, allowing it to be pulled out and restoring blood flow in intracranial vessels during acute ischemic stroke. Interim results were presented from the ongoing, North American, multicenter Multi-MERCI trial,

Multi-MERCI Trial Results

Measurement	Multi-MERCI n=42
Symptomatic hemorrhage	9.5%
Subarachnoid hemorrhage (SAH)	2.4%
Primary endpoints	
Retriever revascularization	57.1% (p<.0001)
Retriever adjunctive revascularization	69.0%
Procedure-related serious adverse events	14.2%
Symptomatic hemorrhage within 24 hours of treatment	9.5%
Symptomatic subarachnoid hemorrhage within 24 hours of treatment	2.4%
mRS ≤2 at 90 days	25%
Key secondary endpoints	
Asymptomatic hemorrhage within 24 hours of treatment	35.7%
90-day mortality	33.3%
Asymptomatic subarachnoid hemorrhage	7.4%

which is looking at the safety and efficacy of the second-generation MERCI Retriever-LX in patients who failed treatment with t-PA. MERCI Retriever-LX and -X6 are both FDA-approved for use in patients ineligible for IV t-PA or refractory to it. Researchers reported on 42 of the 114 patients enrolled so far in this North American trial, and the results looked good compared to the earlier version of this device, but a speaker commented, "In my opinion, it (Retriever) should never have been approved."

Researchers reported:

- There was one asymptomatic procedure-related complication (2.4%).
- A 57.1% revascularization rate, which was the primary endpoint. This is higher than the recanalization rate seen with the earlier Retriever-X5 and -X6 devices. The conclusion was that the primary endpoint is likely to be achieved when the trial is completed.
- Serious adverse events were higher than in the pivotal MERCI trial, with 7.1% device related. This excess of procedural adverse events was described as "concerning." These were not related to t-PA, but may be related to protocol violations.
- IV t-PA therapy does not alter the ICH rate.

DAIICHI

Daiichi has a serotonin agonist in development which researchers believe can be given as late as nine hours after the onset of a stroke.

Diazepam

A speaker suggested that diazepam treatment is safe in acute ischemic stroke but probably should be avoided in ICH. This was based on the results of the three-month, European, multicenter, randomized, placebo-controlled, double-blind EGASIS trial of diazepam vs. placebo in the acute phase of stroke, which looked at pre-specified subgroups. An investigator explained that only 880 of the planned 2,500 patients were enrolled due to opioid importation restrictions. Patients received 10 mg diazepam by recticole as soon as possible, followed by 10 mg BID at 12 hour intervals for three days (six doses). The conclusions were:

- Diazepam treatment is safe in the acute phase of ischemic stroke but probably should be avoided in ICH.
- In acute ischemic stroke, diazepam may increase the chance of favorable outcome by 20%-30%, and perhaps even more in patients with a cardioembolic source.
- Diazepam treatment in acute ischemic stroke deserves further attention.
- There was no effect on consciousness.

3-Month EGASIS Trial Results

Measurement	Diazepam 10 mg	Placebo	Odds ratio
Time to treatment			
<3 hours	19.2%		---
3-6 hours	42.2%		---
6-12 hours	38.6%		---
ITT analysis (843 stroke patients + 6 non-stroke patients)			
Primary endpoint: mRS <3 at 3 months	52%	49%	1.14
Secondary endpoint: Barthel Index ≥95 (complete recovery)	47%	43%	1.16
Any adverse event	~33%	~33%	Nss
843 stroke patients			
mRS <3 at 3 months	52%	48%	1.20
Complete recovery	47%	43%	1.25
748 infarct patients			
mRS <3 at 3 months	53%	48%	1.31
Complete recovery	50%	42%	1.45
Deaths	9.7%	11.4%	---
95 ICH patients			
mRS <3 at 3 months	39%	49%	0.61
Complete recovery	26%	49%	0.33
Deaths	22%	12%	---
200 cardioembolic patients			
mRS <3 at 3 months	50%	36%	2.26
Complete recovery	42%	31%	2.04
Rankin score 0 or 1	30%	21%	2.65
Any adverse event	~50%	~50%	Nss

FERRER'S citicoline

The mechanism of action of citicoline is not well understood, but it was described as a "membrane stabilizer." Citicoline is being explored both in acute stroke and in mild cognitive impairment (Alzheimer's Disease). Indevus used to be Ferrer's partner for this drug but backed out after the ECCO 2000 trial missed its primary endpoint.

Animal studies were described as positive, and a meta-analysis of completed citicoline trials is reported to have shown a 10.4% treatment benefit, with mortality identical, and no significant difference on NIHSS. Ferrer still has confidence in this agent, and a pre-IND meeting is scheduled with the FDA in August 2005, with ICTUS, a 1600-patient, double-blind, multicenter, placebo-controlled Phase III trial due to start in September or October 2005. The dose being used is 2000 mg/day (given in 1000 mg ampoules or 500 mg tablets). For the first three days, patients can get either IV or oral therapy, but after that they will all get oral therapy. Patients can also get t-PA, but investigators do not expect this to be balanced between the drug and placebo arms, so it should not confound the results. The trial will include six weeks of therapy, and

then another six weeks of follow-up. There are three primary endpoints: NIHSS, mRS ≤1, and Barthel Index ≥95. There are numerous secondary and safety endpoints. The trial is expected to take 30 months to enroll, so it is not expected to be completed until 2008.

GLAXOSMITHKLINE'S Fraxiparine (nadroparin)

Nadroparin, a low molecular weight heparin (LMWH), is approved outside the U.S. to treat deep vein thrombosis, and Glaxo is seeking U.S. approval. At ESC, researchers presented results from the open label, multicenter, randomized FISS-tris study comparing nadroparin to aspirin in acute ischemic stroke patients with large artery occlusive disease (LAD). It was conducted in Singapore and Hong Kong. All patients got 80-325 mg aspirin for six months after the trial. The goal was to show the superiority at six months of a 10-day regimen of subcutaneous nadroparin 0.4 mg BID over 160 mg aspirin QD. However, overall, the trial showed no superiority for either nadroparin or aspirin, and researchers declared it a "neutral" study.

FISS-tris Trial Results in LAD Patients

Measurement	Aspirin n=173	Nadroparin n=180	p-value
Median time to treatment	28 hours	28 hours	---
Treatment received within 24 hours	42%	37%	---
Primary endpoint: Barthel Index ≥85	69%	73%	Nss
Died or Barthel Index <80	31%	27%	Nss
mRS 0	0	6%	Nss
mRS 1	38%	45%	0.05
Secondary endpoint: mRS 0 or 1	38%	51%	<.05
MMSE at 6 months	23.3%	24.7%	.057
IST at 6 months	54%	62%	Nss
NIHSS	N/A	N/A	Nss

Magnesium sulfate

The FAST-MAG trial is testing administration of $MgSO_4$ by paramedics in the ambulance, with the hope that a field treatment delay of <30 minutes vs. treatment at the hospital in >3 hours will produce improved outcomes. The expectation is for a median delay in treatment of 90 minutes, with 33% expected to be treated in <1 hour. There is no prior imaging before treatment, and the trial accepts that some patients will not later be found to have had a stroke. The trial also assumes treatment in less than two hours will outweigh any misdiagnoses. The functional endpoints are: 1) Barthel Index ≥95, and (2) mRS ≤1.

NOVO NORDISK'S NovoSeven (rFVIIa)

This prothrombotic hemostatic agent targeted at intracerebral hemorrhage already is approved in some countries, including the U.S., to treat hemophiliac bleeding. A small, 48-patient, Phase II safety and feasibility study in stroke found no major safety concerns, and further trials were begun to test whether Factor VIIa can effectively limit ICH growth.

At ESC, researchers reported on a post-hoc analysis of Factor VIIa in a prospective, 399-patient trial in spontaneous ICH. A researcher said, "An interesting result – and we don't know what it means yet – is that mortality increased with higher doses of Factor VIIa. Factor VIIa does create a tighter clot." A doctor in the audience commented, "There could be harm here. We need to measure if the drug gets into the ventricle. It sounds like the drug…doesn't prevent new bleeding into the ventricle, and it doesn't prevent expansion, but it was beneficial even if the patient had blood in the ventricle."

The first patient was enrolled on May 11, 2005, in the Phase III FAST trial. In this trial, patients will be able to get the drug up to four hours after stroke onset. Patients must get a CT scan before use of the drug. The primary endpoints are mRS and Barthel Index. An official suggested this may be able to be used along with AstraZeneca's Cerovive, but that is not being tested yet.

PAION/FOREST LABORATORIES' desmoteplase

This enzyme from a vampire bat, which Paion licensed from Schering AG, is now going into Phase III. Phase II data look promising, with the drug effective up to nine hours after the onset of a stroke. Desmoteplase has been granted fast track status by the FDA, and Paion and Forest hope to submit the NDA in 2007.

The first Phase II trial in acute ischemic stroke, DIAS, suggested desmoteplase is efficacious and safe. Part 1 of the DIAS trial was stopped early because of an excess of bleeding, and Part 2, using escalating doses, appeared to resolve the bleeding problem. A second Phase II trial, DEDAS, showed similar results, but only at the higher dose (125 µg/kg). The lower (90 µg/kg) dose did not show statistically significant efficacy as in the DIAS trial. Both trials were MRI-based.

A pooled analysis of these two trials was presented at the ESC meeting. Researchers concluded:

- The primary endpoint of MRI reperfusion at 4-8 hours in responders was not statistically significant.
- It appears to be a safe drug.
- There was no increase in symptomatic ICH or mortality in patients treated 3-9 hours after stroke onset with either 90 µg/kg or 125 µg/kg IV desmoteplase.
- Reperfusion and clinical outcome were significantly improved by 125 µg/kg desmoteplase vs. placebo. There

was a trend toward improvement with the 90 µg/kg dose, justifying further investigation of that dose.

- A subset analysis found less discordance between the two trials than the ITT analysis showed.
- Efficacy appeared independent of the time window of administration (3-6 hours vs. 6-9 hours).

The next step is the pivotal Phase III DIAS-2 trial, which is due to start in the summer of 2005. It will prospectively compare patients with perfusion CT vs. MRI.

♦

Meta-analysis of DIAS and DEDAS Trials of Desmoteplase

Measurement	Placebo n=35	Desmoteplase 90 µg/kg n=29	Desmoteplase 125 µg/kg n=30
Symptomatic ICH rate	0	3.4%	0
Mortality	5.7%	6.9%	3.3%
Primary endpoint: **MR perfusion at 4-8 hours** *(TIMI improvement by ≥2 points or PWI lesion reduction by ≥30%)*	20.0%	38.1%	68.0%
Clinical response at 90 days *(NIHSS improvement >8 points or scoring 0-1 AND mRS 0-2 AND Barthel Index 75-100)*	19.4%	43.5%	65.4%