Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Several new agents look promising to treat anemia, including Affymax's Hematide, Roche's CERA, and FibroGen's FG-2216 and FG-4592. ♦ Nabi Biopharmaceuticals may abandon StaphVax, but Keryx is not giving up on sulodexide in diabetic nephropathy. ♦ Abbott's oral Zemplar isn't generating any excitement and usage is increasing very slowly. ♦ Amgen's Sensipar is catching on, but it is having less effect on use of vitamin D or Genzyme's Renagel than was predicted. ♦ The DCOR Renagel mortality study didn't impress most experts, but it may be a useful marketing tool. ♦ Also worth watching: FibroGen's FG-3019 (CTGF) for renal fibrosis, and Speedel's SPP-301 for diabetic nephropathy. ♦ Nephrologists were not concerned with new CMS anemia drug reimbursement regulations.

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

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New therapies for anemia – such as Affymax's Hematide, Roche's CERA, and FibroGen's FG-2216 – were a key topic at this year's Renal Week, and doctors reported on early experience with some recently approved agents, such as Amgen's Sensipar, Shire's Fosrenol, and Abbott's oral Zemplar. New data also were presented on established therapies, including Genzyme's Renagel and Amgen's Aranesp. Medicare reimbursement changes were announced during the meeting, and regulators discussed those and other issues.

ANEMIA

AFFYMAX'S Hematide

This synthetic peptide-based erythropoiesis-stimulating agent (ESA) is unrelated to erythropoietin (EPO), and it doesn't have the potential to cause PRCA (pure red cell aplasia). It is administered once-monthly. Three Phase II trials are ongoing:

1. A U.S. trial in hemodialysis patients of an IV formulation.
2. A European study in pre-dialysis patients of subcutaneous administration.
3. A 30,000-patient trial in pre-dialysis patients that is almost finished.

The end-of-Phase II talks with the FDA are expected to occur in 4Q06. A Phase II trial in oncology was due to start by the end of 2005, and Phase III was to start in late 2006. An Affymax official said the dose may be lower in pre-dialysis because patients with reduced kidney function may clear Hematide slower. Company officials insisted there are no patent issues with Amgen.

A researcher suggested these advantages over EPO:

- No cross reactivity with EPO. No antibodies but no PRCA potential. In fact, a source suggested Hematide may "rescue" PRCA patients.
- Not recombinant. It is synthetic, and easier to make than EPO. However, Hematide is expected to be priced "competitively" vs. EPO.
- Stable at room temperature. It does not have to be refrigerated.
- Once-monthly dosing.

Compared to FibroGen's FG-2216, Hematide was described as offering:

- Less frequent dosing.
- Less variability of response.
- Doesn't stimulate VEGF as FG-2216 does.
- Affects fewer pathways.
- Lower pill burden.

AMGEN Aranesp (darbepoetin alpha)

An Amgen official said the company still needs to educate doctors about dose titration for Aranesp, but Aranesp use is benefiting from:

- Increased treatment penetration.
- Increased provider base. Currently fewer than 50% of pre-dialysis patients get Amgen's Epogen. Of the 2.2 million CKD sufferers estimated to have anemia, only about 1.1 million have been diagnosed, and 60% of these are seen by internal medicine doctors or primary care physicians. Amgen recently launched a Primary Care pilot to see if primary care physicians can start Aranesp. Early results indicated a "nice change in attitude by physicians."

Potential new indications for Aranesp include:

- Monthly dosing.
- CKD Stage 3-4 patients.
- Diabetes. TREAT, a randomized, double-blind, 4,000-patient heart failure outcomes study, is actively enrolling patients with CKD, Type 2 diabetes, and anemia. The primary endpoint is a composite of all-cause mortality or non-fatal cardiovascular events, including myocardial infarction, myocardial ischemia, stroke, and heart failure.
- Heart failure.
  - Data will be presented at the American College of Cardiology meeting in March 2006 on three completed Phase II trials in heart failure, with a total of >500 patients with symptomatic heart failure and anemia, comparing Aranesp to placebo for up to one year.
  - The protocol for a Phase III trial of Aranesp in heart failure is being finalized, and the trial will start in 2006, with 34-month follow-up.

An Amgen official said the objectives for Aranesp include:

- Highlighting the prevalence of CKD and anemia in CKD.
- Filing Aranesp by the end of 2005 for extended dosing, "focusing on once-monthly maintenance therapy."
- Evaluating the impact on mortality and morbidity in anemic patients with CKD in a heart failure trial to start next year.

AMGEN'S Epogen

An Amgen official predicted, "We will continue to see growth in free-standing dialysis centers of about 4%. We have seen a year-to-year decline in Epogen (sales) – some due to changes in wholesaler inventory, and some due to hospital switches to Aranesp. We estimate we will sell $150-$200 million of Aranesp in dialysis this year."

The official outlined three growth areas for Epogen:

1. New patients (~4% a year).
2. Post-hospitalization patients, which is the area he believes is most likely to see sales growth.
3. Patients with hemoglobin <10. It was estimated that 5%-6% of American patients are in this category.

FIBROGEN'S FG-2216

FG-2216 is an oral small molecule inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) which (1) regulates transcription of the erythropoietin gene and utilization of iron and (2) overcomes inflammatory suppression of erythropoiesis. FG-2216 is often referred to as an "oral EPO," but FibroGen officials were quick to point out that this is not a correct characterization. FG-2216 is oral, but works by stabilizing HIF and thereby promoting endogenous production of erythropoietin. FG-2216 does not act on the EPO receptor directly.

Currently FG-2216 is in tablet form, with doses of 125 mg, 250 mg, and 500 mg. Patients take 1-2 pills per dose.

A poster presented a four-week comparison of FG-2216 vs. Aranesp in a rat model of anemia of chronic disease. The study found that FG-2216, given intermittently (three times a week) significantly alleviated the anemia and improved the microcytosis, while IV iron and Aranesp given Q2W did not. Another poster reported that, in lung and colon tumor models, FG-2216 increased EPO and/or hematocrit (HCT) and did not increase primary tumor growth or metastasis. Researchers concluded that the findings support use of FG-2216 in treatment of human cancer-related anemias and other anemia of chronic disease indications.

Experts outside FibroGen who were questioned about FG-2216 described it as promising, but they said it is way too early to determine the outlook for this agent. They stressed that much more data are necessary – but agreed that an oral agent, especially one given once monthly, would be very appealing to patients. An Ohio doctor said, "People are skeptical because HIF affects more than one gene, but it is a promising new concept to pursue." A Michigan doctor said, "FG-2216 raises hemoglobin a little faster than Epogen, but I think there is a steep dose response curve with a lot of variability."

Dr. David Liu, Vice President for Research at FibroGen, called FG-2216 "EPO to the power of 3," citing three key features:

1. Endogenous EPO.
2. Mobilizing and utilizing iron.
3. Overcoming inflammatory suppression of erythropoiesis.

The advantages of FG-2216 also include:

- **Intermittent dosing.** The company has been testing three-times-a-week dosing, but it expects to be able to do once-monthly or even less frequent dosing. If three-

times-a-week dosing is necessary, the company suggested it might offer the pills in a pack with placebos on the other days, similar to the way some birth control pills are dispensed.

- **Dual action – on erythropoiesis and on iron.** He said the effect on iron may be just as important as anemia correction in CKD patients, "Our therapy not only increases endogenous EPO but also maintains a balance of iron stores and mobilizes and allows proper utilization of intrinsic iron stores without iron supplementation…Not only do you obviate the need for IV iron…but the iron that is now being used is endogenous iron. We are resetting the equilibrium, so there are not as many peaks and troughs."
- **Cost.** While FibroGen officials would not say what FG-2216 will cost, they repeatedly insisted it will be priced "quite a bit cheaper" than Epogen, Aranesp, Johnson & Johnson's Procrit, or generic EPOs. In addition, FG-2216 users may save on IV iron costs.
- **Effect in patients refractory to EPO.** "In the setting of chronic inflammation – which is several million people who are anemic and don't respond to EPO – we have shown, preclinically, that FG-2216 can overcome this in ***all*** the animals…In an anemia of chronic inflammation model, where IV iron or recombinant EPO or the two together are not effective in raising hemoglobin, FG-2216 is…There are dialysis patients, rheumatoid arthritis patients, IBD, and lupus patients where EPO doesn't work. And there are millions of people with anemia of aging and CHF who are being treated by general practitioners."
- **Safety.** Dr. Liu said, "In animal models, EPO depletes iron and has thrombosis issues…What has been dogma is that thrombosis is caused by sluggish blood flow caused by high levels of hemoglobin and red blood cell content …so the patient is more susceptible to coagulation… There is also more evidence that EPO itself, as a hormone, can activate parts of the clotting mechanism… So, you could have high levels of EPO circulating, and that may be enough to create pro-thrombotic situations in certain situations…The amount of EPO we induce is much, much less."

The disadvantages or concerns with FG-2216 include:

- **Variability in response.** However, it is early in the design of dosing regimens, and this may be resolved with further studies.
- **Side effects.** Similar to EPO – transient headaches that are not dose-related and nausea. However, the rates were reported to be similar to placebo rates.
- **Thrombosis.** There was some thrombosis seen with very high level doses in early toxicology studies, but the company expects the thrombosis risk to be much lower than EPO when final dosing is determined.
- **Likely need for a partner.** FibroGen has already partnered with Astellas (formerly Yamanouchi) in Japan. Dr. Liu said, "We think some aspects we can do ourselves. When we consider the expenses and timeframe for commercialization of the product in the general practitioner setting, then perhaps a partner may be needed." A parallel program is ongoing in Japan, and FG-2216 is already in clinical trials there.
- **VEGF effect.** Some competitors suggested that FG-2216 up-regulates VEGF, which likely would be a negative effect, but the company said its studies have found no increase in VEGF with FG-2216. Dr. Liu said, "We think FG-2216 is preferential for HIF-2, and it is HIF-1 that up-regulates VEGF."
- **Unknown effect on other HIF actions.** HIF has effects on a number of pathways, and some doctors expressed concern that so-far-unseen side effects will come up with more and longer use of FG-2216.

FibroGen officials were insistent that Amgen's EPO patent will not affect FG-2216 or the company's other agents. Dr. Liu said, "We do nothing directly with the EPO gene. We are modulating HIF…We don't work directly – only indirectly – with the EPO gene."

What is the next step for FG-2216? More and longer Phase II trials, including dose titration studies, comparing FG-2216 to placebo. Dr. Liu said, "We need more patients to build up the database, and we need to find the optimal dosing level and schedule."

- A planned U.S. Phase IIb trial will follow patients for 3-4 months.
- A European Phase II trial was recently finished and was reported at the American Society of Hematology in December 2005.
- A Phase III U.S. trial is unlikely to start before 2007 or 2008 and will depend on the results of the Phase II trials.
- Development would be faster in EPO-non-responsive patients, since that is an unmet medical need, and the company is considering that.
- No cancer trials are currently planned.

At the American Society of Hematology meeting, in early December 2005, FibroGen presented more data on FG-2216, this time from a preclinical, dose-escalation study in chronic anemia in primates. In the six-month study, conducted by the

6-Month Results of FG-2216 in Primates with Chronic Anemia

Measurement	FG-2216 40 mg	FG-2216 60 mg
Increase in hemoglobin from baseline at 60 days	1.2 g/dL	2.6 g/dL
Average hemoglobin level after 2 months of Q2W dosing	N/A	>2.5 times placebo levels

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Heart, Lung, and Blood Institute (NHLBI), FG-2216 was shown to be safe and well-tolerated, dose-dependently stimulating increases in hemoglobin levels, and preventing reductions in hemoglobin levels due to phlebotomy. There were no clinical adverse events or significant changes in serum chemistry or renal or hepatic parameters reported.

FibroGen's FG-4592

FG-4592 is FibroGen's second generation oral anemia compound. Officials said it is more potent than FG-2216 and may have benefits in anemia of chronic disease. FibroGen has not yet sorted out whether there are different optimal benefits or patient populations that respond to FG-4592 vs. FG-2216. Dr. Liu said, "This (FG-4592) gives us the ability and flexibility to move into other indications…We believe it (FG-4592) will be a good candidate for anemia of chronic disease."

Asked how FG-4592 differs from FG-2216, Dr. Liu said he couldn't make a good differentiation yet, except on potency. He said, "FG-4592 is not a replacement for FG-2216 but is a contingency…First, if FG-2216 were to fail, we have the ability to move this forward. Second, it looks very potent so far…In the end, it will be the clinical data that say what the differences really mean...beyond FG-4592 being more potent."

FG-4592 can be given daily, with a dose-dependent increase in erythropoiesis. Researchers reported that a single, oral dose of 0.3 µg/kg in healthy male volunteers caused a small increase in erythropoiesis, and a 1.0 µg/kg dose results in a significant increase in erythropoiesis. A speaker said, "It is efficacious even when erythropoiesis is suppressed by chronic inflammation." He said FG-4592 has not yet been studied in infected animals.

FG-4592 in Monkeys with Anemia of Chronic Disease

Measurement	IV Iron 1.5 mg/kg/week	Aranesp 30 µg/kg	FG-4592 40 µg/kg
Hemoglobin change from baseline	Up ~4 g/dL	Up ~10 g/dL	Up ~38 g/dL
Mean cell volume change from baseline	Down ~24 fL	Down ~10 fL	Up ~24 fL

Roche's CERA

During ASN, Amgen filed suit against Roche, alleging CERA infringes Amgen's patents for Epogen, seeking a permanent injunction barring the manufacturing, importing, use, or sales. Roche issued a statement saying, "We are confident that CERA does not infringe any of Amgen's U.S. patents for epoetin. We are reviewing Amgen's allegations, but whatever our decision regarding the litigation, Roche is committed to developing CERA and pursuing U.S. FDA market approval for CERA as well as approval around the world. CERA was granted a patent in the U.S. in 2003, thus acknowledging it is novel and useful." An expert said, "The patent dispute could go either way…In a nutshell, CERA is a pegylated EPO." A Roche official said CERA is mechanistically different from Epogen, "CERA has on and off binding to the outside of the receptor and is not internalized vs. EPO which binds irreversibly and is internalized and then, hypothetically, it (EPO) is believed to be metabolized."

A U.K. researcher described CERA as "smoother, with more sustained hemoglobin." He said the advantage to CERA will be in pre-dialysis and transplant patients, "Dialysis patients come in three times a week, so there is less advantage to once-monthly dosing with them, and that could slow adoption." A Michigan nephrologist said, "If priced the same as Epogen, CERA would cost less because the administrative costs would be lower, and it would save on nursing time and documentation…I would switch patients to CERA, not just use it for new patients. If it were cost neutral, I would still use CERA for both dialysis and pre-dialysis patients. If pre-dialysis patients, you could probably use it even less frequently than once a month because that makes sense – not if a patient is close to dialysis, but in earlier stage you could perhaps dose every two or three months."

Roche officials cited these possible advantages of CERA over EPO:

- Once-monthly dosing for dialysis patients.
- IV and subcutaneous use the same dose, which improves convenience and could be a significant factor in Europe.
- Long half-life (≤134 hours at the 0.4 µg/kg dose), but reliability between intervals.
- Stability of hemoglobin.
- Theoretically, CERA may have less hypertension.
- Could be more successful in treating patients to goal with less fluctuations and a less rapid hemoglobin rise.
- CERA might fit well into a CMS bundling project.

Several studies of CERA were presented at ASN, including:

1. An open-label, randomized, single-center, single-dose, three-way crossover PK study in 42 healthy volunteers. Researchers found that CERA probably can be administered subcutaneously in a variety of injection sites:
   - Single doses of subcutaneous CERA, administered in the abdomen, arm, or thigh, elicited similar serum CERA profiles, including a prolonged elimination half-life (mean ~160 hours).
   - CERA induced a sustained erythropoietic response that was similar in magnitude regardless of the site of administration.
   - All sites of administration were well tolerated.
2. An 18-week, open-label, randomized, multicenter, Phase II dose-finding study of SQ CERA in 65 CKD patients not on dialysis found a dose-dependent reticulocyte response. The erythropoietic response was independent

of the frequency of CERA administration. Again, the results support administration at extended intervals.

3. A 12-month extension study of an open-label, randomized, multicenter, Phase II study looked at SQ CERA in 51 CKD patients not on dialysis. Researchers reported that SQ CERA:
   a. Provided sustained and stable control of hemoglobin levels when administered at extended intervals of up to once every three weeks.
   b. Maintained long-term control of hemoglobin levels over 12 months.
   c. Was generally well tolerated. The most frequently reported adverse events were urinary tract infections (5.2%), gout (3.4%), hypertension (3.0%), and peripheral edema (3.0%).
4. Another study evaluated subcutaneous and IV CERA in 16 peritoneal dialysis patients. The study found the half-life was comparable for SQ and IV administration, suggesting extended administration intervals are feasible.

CERA in Peritoneal Dialysis Patients

Measurement	IV CERA	SQ CERA
C_{max}	9.05 ng/mL	4.60 ng/mL
AUC_{last}	1028 ng.h/mL	1106 ng.h/mL
Half-life	134 hours	139 hours
Clearance	0.494 mL/h/kg	0.899 mL/h/kg
Bioavailability	100%	52%

On December 16, 2005, Roche announced successful completion of all four pivotal Phase III clinical trials for CERA. Another two studies examining correction of anemia in patients with chronic kidney disease on dialysis and not on dialysis are nearing completion. The Phase III data could be presented at the National Kidney Foundation meeting in Chicago in April 2006, but it is more likely to be at European Dialysis and Transplant Association (EDTA) in Glasgow in July 2006. Roche said it plans to submit CERA simultaneously to U.S. and European regulatory authorities in 2006 for once-monthly dosing, and a launch is expected in early 2007.

DIABETIC NEPHROPATHY

KERYX BIOPHARMACEUTICALS' sulodexide (KRX-101)

This oral glycosaminoglycan has been approved in Europe since 1982 as an antithrombotic. The mechanism of action in the kidney is unknown. A Phase II study reported earlier this year did not meet its primary endpoint, and there was no dose response curve.

However, a randomized Phase III trial in Type 2 diabetics with microalbuminuria was still started in August 2005 in the U.S., the Netherlands, Australia, and Israel, and a second large study also is underway. The run-in in the Phase III trial (which uses only a 200 mg dose) was increased from 2 to 3 months with ARBs to be sure patients are absolutely stable before sulodexide is administered. A source said he is concerned the trial is "horribly underpowered."

The results of the 135-patient Phase II trial were presented at ASN. A Keryx researcher at ASN insisted this was ***not*** a failed trial. In the trial, all patients got ACE/ARBs. A speaker also called this a "very underpowered study," adding sulodexide was associated with decreased urine albumin excretion, which was maintained for two months after cessation of therapy. The speaker concluded, "This pilot trial confirms the efficacy of sulodexide in terms of its ability to induce a decrease in albuminuria in the treatment of patients with early Type 2 diabetic glomerulopathy."

Sulodexide Phase II Results

Measurement	Placebo n=47	Sulodexide 200 mg n=50	Sulodexide 400 mg n=52
Average weight	220	206	209
HbA_{1c}	7.4	7.5	7.6
Primary endpoint: 50% decrease in microalbuminuria	~12%	25%	
Normal albuminuria	8%	16%	

SPEEDEL'S SPP-301

SPP-301 is a once-a-day oral endothelin-A receptor antagonist (ERA) licensed from Roche. When given on top of standard treatment (ACEi or ARB), it was reported at ASN to reduce the urinary albumin excretion rate (UAER) and total cholesterol in patients with diabetic nephropathy. The results came from a 12-week, 286-patient, randomized, double-blind, parallel design, dose-ranging (5 mg, 10 mg, 25 mg, and 50 mg), European Phase IIb trial in mostly Type 2 diabetics.

Compared to placebo, all doses of SPP-301 decreased UAER significantly ($p<0.001$), with the highest two doses (25 mg, 50 mg) demonstrating the greatest reduction in UAER. There was also a significant reduction in total cholesterol at all doses ($p<0.001$) vs. placebo. SPP-301 also was shown to reduce proteinuria by ≥30% for 55% of all patients across all dose groups.

Although other ERAs in the past have been associated with liver toxicity, there has been no indication of this problem so far with SPP-301.

A 3.5-year, pivotal Phase III trial, ASCEND, began in July 2005 in Europe, the U.S., and other countries, and should be completed at the end of 2008. This is a randomized, placebo-controlled study with >2,000 patients, designed to assess time to doubling of serum creatinine, ESRD, or death in Type II diabetics with nephropathy. The FDA has granted Fast Track status for SPP-301 in diabetic nephropathy under a Special Protocol Assessment.

PHOSPHATE BINDERS, VITAMIN D ANALOGS, AND CALCIMIMETICS

ABBOTT'S Zemplar (paricalcitol), a vitamin D analog

IV Zemplar is a well-established vitamin D analog, and almost every nephrologist questioned is using it. However, oral Zemplar has gotten off to a slow start. This is not surprising, given the predictions of doctors at ASN two years ago. An official with a renal chain said, "We don't use oral Zemplar because the IV works better." A Kentucky doctor said, "We use Hectoral (Genzyme, doxercalciferol) because we have experience with it, but we are starting to use a ***little*** oral Zemplar."

Some studies have shown a survival advantage with vitamin D, but speakers said additional data are needed. Audience answers were interesting at an Abbott-sponsored lunch on vitamin D.

Audience Perception of Vitamin D Action

Answer	Before lecture	After lecture
Vitamin D is associated with increased vascular calcification.		
True	57.9%	35.2%
False	42.1%	64.8%
Which is associated with increased vitamin D receptor activation?		
Reduction in renin expression	0.5%	1.4%
Decrease in PTH expression	21.4%	3.4%
Stimulation of calcium sensing	5.1%	1.4%
Regressions of left ventricular hypertrophy	0.5%	0
All of these	72.6%	93.9%
Is there any difference among the various vitamin D compounds?		
Yes	86.9%	83.0%
No	13.1%	17.0%
Is there any relationship between vitamin D and cardiovascular disease?		
Yes	88%	84.7%
No	12%	15.3%

AMGEN'S Sensipar (cinacalcet), a calcimimetic

An Amgen official said that doctors are using Sensipar, both with and without vitamin D, and that they were using it primarily in more severe patients but are now using it in more mild-to-moderate patients. She also predicted that the Medicare Part D drug benefit will "give a boost" to Sensipar use, "One-third of eligible patients don't have (drug) coverage today, so we think that will accelerate growth."

The average Sensipar dose today is ~43 mg in all-comers, but an Amgen official said this is due to the influx of new patients, which lowers the average, and the official predicted the average dose may go down further as more patients with milder disease are put on Sensipar. In patients who have been on Sensipar 6-12 months, the average dose is 55-60 mg, which is unchanged from last year. A clinician added, "We are early in the evolution of physician understanding and acceptance of Sensipar…There is often a delay in titration." A Colorado nephrologist said, "It takes a lot of work to use Sensipar, and the effect on outcomes is not clear."

Use of vitamin D and Renagel with Sensipar is still evolving. A doctor said, "When a patient gets hypercalcemia, I either ignore it, hold the drug, or back off a little. I thought Sensipar would reduce vitamin D use, but it really didn't change our use, but perhaps that is because we were conservative with vitamin D before."

At ASN, Amgen data showed Sensipar:

- Reduces PTH and Ca x P for more than two years.
- Achieves KDOQI guidelines with reduced vitamin D use in the START study.
- Results in a 3.9% absolute reduction in vitamin D use (in one study).
- Showed a 39% reduction in cardiovascular events vs. placebo (p=.005) in a pooled analysis of Phase III data.

An animal study found that Sensipar probably would not be an effective agent in the treatment of idiopathic hypercalciuria in humans. Hypercalciuria is the most common metabolic abnormality in humans with nephrolithiasis.

Planned studies for Sensipar include a definitive outcomes study of the treatment of secondary HPT designed to see if Sensipar reduces the risk of mortality and non-fatal CV events in dialysis patients. The trial will enroll ~1,900 patients on Sensipar and another ~1,900 on placebo – and all will be allowed flexible vitamin D and phosphate binder use. The trial is expected to take 1.5 years to enroll, and follow-up will be 2.5 years.

Asked about an ASN debate on the value of calcium-based phosphate binders, a clinician made an indirect criticism of Genzyme's DCOR study of Renagel (sevelamer), saying, "I would highlight how impressed I am with Amgen's commitment to doing well designed, well-powered, long-term studies. As the discussion evolved during the (debate) hour, you could see how complex the situation is…It is essential to do landmark clinical trials…and I'm very excited about Amgen's commitment to that."

A retrospective study by researchers at SUNY Stoneybrook looked at 42 dialysis patients. At baseline, most were on Genzyme's Hectoral (vitamin-D pro-hormone) and various calcium and non-calcium phosphorous binders.

Sensipar Effect on Other Drugs After 6 Months

Measurement	Before Sensipar	After Sensipar
Renagel use	14,296 mg/day	8,560 mg/day
Hectoral	62.1%	75.9%
Calcium acetate	2,219 mg/day	4,802 mg/day

Asked about the FDA approvable letter for Sensipar in pre-dialysis patients, an Amgen official said the letter followed a filing on Phase II data, but a Phase III study is now planned. The Phase III trial will be an active-control study of Sensipar given on top of vitamin D and phosphate binders, which is similar to the Phase III trial for initial approval of Sensipar. A nephrologist commented, "I think it will be approved in pre-dialysis because it clearly works in those patients."

GENZYME'S Renagel (sevelamer hydrochloride), a phosphate binder

The three-year results of the DCOR trial of Renagel vs. calcium were presented in a poster and discussed at a very large and very well-attended dinner sponsored by Genzyme. Doctors in the audience appeared fairly impressed with the data and predicted it would make it harder for insurers to deny payment. The bottom line in DCOR was that all-cause mortality is statistically significantly better with Renagel ***only*** in patients who are over age 65 or who are on the drug ≥2 years – or both.

A Genzyme official said the three messages from this trial are: (1) Patients have to use Renagel >2 years to see a benefit, (2) Patients should be treated early, and (3) The greatest benefit is in older people. DCOR principal investigator, Dr. Wadi Suki of Texas, said 20 patients have to be treated with Renagel to save one life. He said the DCOR message is: Patients must take Renagel more than two years, and the patients most likely to benefit are over age 50.

Dr. Suki said a post hoc analysis by 5-year increments of age found the relative risk reduction in all-cause mortality becomes statistically significant above age 45, regardless of how long the patient took Renagel. He added that the treatment duration effect and lack of effect in patients age <40 may have caused the all-cause mortality to not be statistically significant in patients under age 65 or who took Renagel less than two years. He also noted that an association analysis found a highly significant effect of treatment with Renagel on all-cause mortality (p=.0165).

However, several questions about the analysis could be raised, including:

- The trial did not meet its primary endpoint.
- The dropout rate was 57%; only 43% of patients completed the three years of the trial.
- Statin use was not monitored in trial patients.
- This was not an intent-to-treat (ITT) analysis with last observation carried forward (LOCF). Rather, it was a completers analysis.

3-Year DCOR Trial Results

Measurement	Renagel n=1,033	Calcium n=1,007	p-value	Relative risk
All-cause mortality				
Primary endpoint: Overall	26%	N/A	0.30	0.91
Per 100 patient years	15.16	16.18		
Patients treated <2 years	35% n=587	34% n=587	0.42	1.08
Patients treated ≥2 years	13% n=446	18% n=424	0.02	0.66
Patients age <65	21%	19%	0.31	1.14
Patients age <65 rate per 100 patient years	12.44	10.7		
Patients age ≥65	32%	38%	0.03	0.78
Patients age ≥65 rate per 100 patient years	18.36	23.56		
Other mortality				
Infection mortality	4.5%	4.1%	0.96	1.01
Infection mortality per 100 patient years	2.61	2.42	---	---
Other deaths	7.8%	8.6%	0.32	0.86
Other deaths per 100 patient years	4.42	5.14		
CV mortality	14%	14%	Nss	---
CV mortality per 100 patient years	7.99	8.62	0.48	0.92
CV mortality in patients age ≥65	18%	21%	0.14	0.80
Hospitalizations				
Mean number of hospitalizations	2.1	2.3	0.06	---
Median number of hospitalizations	1.0	1.3	0.06	---
Mean number of days hospitalized per patient	15 days	17 days	0.09	---
Median number of days hospitalized per patient	5.0 days	5.8 days		---
Patients age ≥65 mean number of hospitalizations	2.1	2.9	0.03	---
Patients age ≥65 median number of hospitalizations	1.3	1.6		---
Patients age ≥65 mean days hospitalized per patient year	13 days	14 days	>.50	---
Patients age ≥65 median days hospitalized per patient year	3.4 days	4.0 days		---

3-Year DCOR Trial Laboratory Results and Serious Adverse Events

Measurement	Renagel	Calcium	p-value
Laboratory results			
Phosphorus	5.8	5.7	<.01
Calcium	9.2	9.5	<.0001
Ca x P	53.7	53.6	0.60
iPTH	278	226	<.0001
Total cholesterol	145.6	160.8	<.0001
LDL	69.0	84.9	<.0001
Kt/V	1.6	1.6	0.11
Serious adverse events			
Serious adverse events	3 patients	5 patients	---

Doctors were questioned about the DCOR results. Academics generally found the study unconvincing and lacking in impact. However, some community doctors thought the results were strong enough that insurance carriers will have trouble denying coverage of Renagel. So, Genzyme may be abel to use DCOR for marketing purposes, at least to a limited extent. A Pennsylvania doctor said, "I'm not impressed with DCOR."

Interestingly, another Genzyme-sponsored poster by researchers at Boston University also found a mortality benefit of Renagel over calcium, but a post hoc analysis of the data found the survival advantage was strongest in younger (<age 65) patients. This was a 2,073-patient retrospective study of veterans initiating dialysis at VA hospitals.

Miscellaneous:

➢ A Genzyme-sponsored study found no significant difference in phosphate binding in rats between Renagel and Fosrenol.

➢ A Mayo clinical study found Renagel does not appear a useful treatment for enteric hyperoxaluria. However, the investigator, Dr. John Dillon, said Genzyme has a sevelamer carbonate in development that may be more promising in that disease and he plans to propose a study of the new agent in enteric hyperoxaluria.

➢ Results of the single-blind, multicenter, 114-patient, Italian 12-week CaCSE Study were presented at ASN. Researchers concluded that:

- Renagel has similar efficacy to calcium carbon-ate with less risks of inducing a positive calcium balance.
- The number of pills rather than the binder dose is crucial for obtaining good compliance.
- Compared to American and Northern European dialysis patients, Southern European patients require much less binder dose to control serum phosphate levels, possibly due to difference in diet and/or to better dialysis treatment.
- At the mean dose of 4 g/day, Renagel did not decrease serum bicarbonate levels.
- Patients rarely tolerate more than 10 capsules per day of phosphate binder.

12-Week CaCSE Study Results

Measurement	Calcium n=54	Renagel n=60
Ca x P	46.8 mg^2/dL^2	49.6 mg^2/dL^2
Phosphate	4.82 mg/dL	5.25 mg/dL
Albumin corrected total calcium levels	9.63 mg/dL	9.40 mg/dL
Intact PTH	221 pg/ml	200 pg/ml
Alkaline phosphatase levels	137 U/L	172 U/L
Dose of phosphate binders	3.66 g/day	3.96 g/day

➢ A large, retrospective, survival study in ESRD patients in the VA database found that, compared to patients taking calcium only, Renagel patients tended to be: younger, more likely to be white, more likely to have ≥50% service-connected disability, fewer comorbidities, and better survival.

Renagel Relative Risk Reduction in DCOR Trial

Measurement	Renagel	p-value
All-cause mortality	9%	0.30
All-cause mortality in patients treated ≥2 years	34%	0.02
All-cause mortality in patients age ≥65	22%	0.03
All-cause mortality in patients age ≥65 and treated ≥2 years	54%	<.001
CV mortality	8%	0.48
Number of hospitalizations per patient year	23%	0.06
Number of days hospitalized per patient year	14%	0.09

SHIRE'S Fosrenol (lanthanum carbonate), a phosphate binder

Shortly after ASN, the FDA approved two new doses of Fosrenol – 750 mg and 1.0 g (1000 mg) – which are expected to be available by the end of the year. The higher doses, in chewable tablets, will help patients reduce the number of pills they must take.

Interim results (up to 24 weeks) on 297 patients from an ongoing Phase IIIb study of patient and physician attitudes about the new formulations were presented at ASN.

Another study presented at ASN found Fosrenol was not associated with any clinically significant adverse changes in hematological or biochemical parameters during long-term treatment vs. standard phosphate-binder therapy. There also was no evidence of treatment-related adverse effects on liver function or predisposition to metabolic acidosis in patients receiving Fosrenol.

A poster presented the safety results from an open-label extension of four previous Fosrenol studies – 2 in Europe and 2 in the U.S. Researchers reported that Fosrenol was well-tolerated over six years of treatment, with no new adverse events reported during the study and no increase in the frequency of treatment-related adverse events with increasing exposure to the drug.

Nephrologists questioned about the outlook for Fosrenol use generally said uptake has been slow mainly because insurance coverage is still spotty, not due to concerns about safety or GI toxicity, though some doctors have taken a wait-and-see approach to Fosrenol. Among the comments on Fosrenol usage were:

- *New England:* "We are only using Fosrenol a little because of concerns that it is a heavy metal. This could be the next aluminum. But when we do use it, I haven't seen much GI toxicity."

- *California:* "I only have one Fosrenol patient. It isn't better than calcium carbonate, and it is more expensive."
- *Fosrenol researcher:* "Doctors are starting with a too-low dose, and they are not up-titrating it enough for long enough, so they get discouraged. The new formulation should be a higher beginning dose. My starting dose is 3 g/day, and the average dose in Europe is 2.25 g/day …The GI side effects are the same as reported. What I tell doctors who say patients complain of GI upset is that only one-third of these are probably real, and those patients should take something else…Fosrenol is the preferred Medicaid drug in dialysis patients (in North Carolina), but in California you can't get it without filling out reams of paperwork…Fosrenol is on our formulary, but even within my own group, doctors are not as informed about Fosrenol as they could be."
- *Pennsylvania:* "We have to use PhosLo (Nabi Biopharmaceuticals, calcium acetate) first, then the choice is between Renagel and Fosrenol. Renagel has the upper hand, but Fosrenol use is increasing. Patients and nurses like Fosrenol because it can be chewed, and there is a minty taste even though it is supposed to be bland. Nurses also are crushing Fosrenol over food, and patients love that…I'm not hearing many GI side effects if patients have food in the stomach."

Interim Results of Phase IIIb Study of Patient and Physician Preference and Satisfaction with New Formulations of Fosrenol

Measurement	Response	p-value vs. previous therapy
Patient satisfaction		
With previous therapy	63%	---
At Week 4	82%	<.001
At Week 8	78%	<.001
At Week 24	78%	---
Physician satisfaction		
With previous therapy	60%	---
At Week 4	84%	<.001
At Week 8	85%	<.001
At Week 24	88%	<.001
Preference for Fosrenol vs. previous phosphate-binder therapy		
	Patients	**Physicians**
Overall preference	64%	68%
Preference for new pill burden	63%	---
Ease of administration	58%	---
Compliance	60%	59%
Dosage forms	---	72%
Efficacy	---	60%
Clinical observation	---	65%

RENAL FIBROSIS

The current management of primary Focal Segmental Glomerulosclerosis (FSGS) is based on the theory that the disease is caused by an immune-mediated disturbance in glomerular barrier function. Therefore, most treatment protocols have involved immunosuppressive drugs given singly or in combination, though the efficacy of this type of therapy has been disappointing, and the long-term prognosis for renal survival in patients with resistant FSGS is poor.

There are no markers approved or near approval for renal fibrosis, but several urine markers are being explored, including:

- Urinary aminoterminal propeptide of type III procollagen (PIIINP) as a marker of interstitial fibrosis in renal transplant recipients.
- Urinary excretion of MCP-1.
- Levels of TIMP-1 and tenascin in patients with renal disease. There is not a lot of specificity with this; it is just a general marker of injury.
- Beta Ig-3 in patients with Type 2 diabetes.

Advantages and Disadvantages of Discovery Platforms

Platform	Advantages	Disadvantages
RNA expression	High throughput, commercially available	No information about PTMs, RNA correlation with protein?
2D-PAGE	Quantitative, measures actual marker, unbiased	Poor for membrane proteins, high MW and extreme pH
SELDI	Pattern generation, efficient	Reproducibility, identification
LC/MS/MS	Efficient, identifies membrane proteins	Expense, not many groups proficient
Mass spectrometry (MS) imaging	Studies only pathology	Availability, transfer to clinic?

A speaker noted that:

- **Proteomic analysis.** Proteomics has found that changes in elastin regulation may be a good urinary marker.
- **Mass spectrometry (MS).** A speaker said there is increasing thought that mass spec itself can be quantitative.
- **Gene array, urinary proteins, and mass spec imaging** all need to make the transition to simple antibody-based assays.

Agents on the horizon

Specific agents in development to treat renal fibrosis include:

1. Retinoids. A trial is underway comparing retin-A and Accutane.

2. InterMune's pirfenidone. The mechanism of action of this oral small molecule is unknown, but it may reduce production of TGF-β, antagonize TNF-α signaling, and act as a weak antioxidant. Studies have shown a benefit in animals, and an open label human pilot study enrolled 20 patients but was stopped for various toxicities. A speaker said that, of the 17 patients in this trial who received treatment for an average of 18 months, there was a 35% decline in creatinine clearance, and side effects were generally well tolerated. He added, "This is a very small study, but it compares to the captopril effect in diabetic nephropathy of a 35% effect in creatinine clearance." A Phase II trial in diabetic nephropathy is underway, and a Phase III trial in diabetic and non-diabetic CKD is in the planning stage.

3. Anti-TNF-α vs. PPAR-γ. The Phase I/II FONT study is comparing Abbott's Humira (adalimumab) vs. GlaxoSmith-Kline's Avandia (rosiglitazone) in resistant FSGS.

4. FibroGen's FG-3019 (CTGF). FG-3019 is a fully human IgG1 kappa monoclonal antibody against connective tissue growth factor (CTGF). It is being developed to treat renal fibrosis. Currently, FG-3019 is in a Phase Ib trial in Type 1 and Type 2 diabetics with microalbuminuria (incipient nephropathy). Dr. Liu said, "We believe this is the penultimate step leading to renal fibrosis and scarring and organ failure leading to the need for dialysis and transplantation. Our goal is to delay progression and eventually prevent the need for dialysis." Data from this trial are not expected before the American Society of Nephrology meeting in fall 2006 but could come sooner.

FG-3019 may also have a role in treating other comorbidities associated with diabetes – e.g., reversing or preventing: (a) arterial stiffness, (b) microvascular permeability or edema changes related to diabetes, and (c) CV events due to increased intimal media thickness.

How does CTGF function at the molecular level? A speaker said it is not yet clear, but it may be either as a chaperone or carrier protein or as a modulator of other growth factors. She said CTGF does mediate change to a myofibroblast phenotype, promote dysfunction of myofibroblasts, exert an anti-apoptotic effect on myofibroblasts, function via several different mechanisms, and mediate the fibrotic activity of TGF-β.

8-Week Results of FG-3019 in Type 2 Diabetic Mice

Measurement	3 mg FG-3019 vs. control	10 mg FG-3019 vs. control
Albumin excretion rate	Nss	p<.02
Right kidney weight	p<.02	p<.005
Glomerular volume	Nss	Nss
HbA_{1c}	Nss	p<.05
H_2O intake	Nss	p<.02
Urine output	p<.05	Nss
LDL	Ns	p<.05

Regulatory Issues

The FDA perspective on biomarkers and surrogate markers

Dr. Douglas Throckmorton, a nephrologist and Deputy Director of the FDA's Center for Drug Evaluation and Research (CDER), reviewed the regulatory status of biomarkers for kidney diseases. He said, "I believe renal disease needs a fundamental revision in the way we approach drug development. More than many other areas, this is an area where basic science and identification of targets for therapy is exceptional. It is really at the top of the class in my own opinion, but the development of novel therapeutics has lagged behind other areas…We are at a critical place in time on new therapeutics. It is important to change the way we have been thinking about biomarkers – both about what they can do for us and how to develop them…I would like to convince you to use biomarkers in the absolutely most efficient way. The development of new biomarkers is central focus of ongoing efforts by the FDA…The system we have been using cannot sustain the development of new thera-peutics. We need a re-invigoration of the process from target identification to approval of new therapeutics."

Limitation of current biomarkers, include, according to Dr. Throckmorton:

- The pathway to regulatory acceptance of biomarkers and surrogates is not clear.
- The regulatory system has been focused on empirical testing. Dr. Throckmorton said, "Sponsor use of biomarkers in early development is often not discussed with FDA."
- "Use of biomarkers as 'bridges' between mechanism-based preclinical development and early pharmacology clinical evaluations has not been made clear, with resultant loss of information and clarity."
- No single group (FDA, academia, etc) "owns" the development of new biomarkers/surrogates. "Exploration of new biomarkers is generally ad hoc – a paper here and there – and so it is inefficient. As a consequence, there is no rigorous pursuit of needed data to assess the adequacy of new biomarker(s) for regulatory use."
- Historically, successful surrogates have linked effects on biomarkers (e.g., BP, HIV mRNA) to single effects in large populations. "That is at odds with current goals for individualized therapies. It does not recognize the multi-dimensional quality of clinical responses, and it does not include the possibility of multiple biomarkers providing useful information in aggregate (e.g., a 'biomarker basket')."
- Biomarkers must be used to be accepted.
- The add-on costs in clinical trials have been a significant barrier.
- Analyses of biomarker data collected are often ad hoc.

Dr. Throckmorton called for a collaborative effort in biomarker development. He cited several examples of who the FDA is collaborating on biomarker and surrogate endpoint development, adding, "We need to rethink the generally ad hoc way we have developed biomarkers up to now. There are a lot of opportunities for people and for the nephrology community to interact with FDA. A lot of stakeholders will be interested in doing that…(but) we as an agency need to be careful about intellectual property issues…We need to energize the acceptance, development, and use of biomarkers across the entire spectrum of use. Accomplishing this will require extensive collaboration across many stakeholders. No one entity has all the needed resources."

The NIH perspective on Phase II trials

Dr. Jeffrey Kopp of NIH outlined some minimal efficacy goals that should be met in a Phase II trial.

Minimal Effects Expected in Phase II Trials

Disease	Target effect
Treatment-resistant FSGS	20% CR
Diabetic nephropathy	20% reversion of microalbuminuria to normal
Lupus nephritis or small vessel vasculitis	50%
Time to ESRD	50% increase in any progressive kidney disease

Dr. Kopp said there are different design options for Phase II trials, and a minimal acceptable efficacy threshold can be set with all of them:

- **Selection design with multiple agent or doses.** This is sometimes referred to as the "Christmas tree" design. The limitations of this design include:
  - Risk of selecting an agent as better than others when the difference is <15%...so true positives and false positives cannot be distinguished.
  - Smallest response probability may not be knowable in advance, making sample significance difficult to estimate.
  - Best not to include standard therapy.
  - May throw out effective therapies.
- **2-stage design with single arm getting the experimental agent.**
- **Screening design: standard vs. experimental agent.**

CMS issues

Medicare Part D. What effect will the Medicare Part D drug benefit have on use of erythropoietins when it goes into effect on January 1, 2006? Amgen officials declined to estimate how many dual eligibles there are, but one official said, "We think that at least one-third of ESRD patients will benefit from Part D. The affordability of things like Sensipar will benefit."

A California doctor predicted that use of all nephrology drugs will go up. Other sources weren't sure how Medicare Part D will affect drug use.

Epogen and Aranesp reimbursement. During ASN, CMS issued a new decision on Medicare reimbursement for Epogen and Aranesp that will go into effect on April 1, 2006. Prior to this new ruling, CMS based reimbursement at dialysis centers on a 90-day rolling average of hematocrit levels. The target to trigger administration of EPO was 37.5, though higher levels could be approved upon medical justification by the treating physician.

Under the new policy for EPO and Aranesp at dialysis facilities, Medicare will not pay for dosages of EPO in excess of 500,000 IUs per month or Aranesp in excess of 1500 mcg per month. Medicare also will not require monitoring be initiated until the hematocrit level reaches 39.0 (or hemoglobin above 13.0). If hematocrit exceeds 39.0, the drug dose must be reduced by 25% compared to the previous month or CMS will reduce the dosage payable by 25%. Beneficiaries, physicians, and/or renal facilities appeal individual cases by submitting medical documentation that they believe justifies the need for a higher hematocrit level. For example, if the patient's hematocrit level in May is 40.0, EPO dose in June should be reduced by 25%. So, if the patient got 10,000 IUs in May, the patient should get only 7,500 IUs in June – or CMS will only pay for 7,500 IUs in June.

Asked if the 25% cut in Epogen/Aranesp for patients whose last hemoglobin of the previous month was >13 is for the entire next month or for the first dose in the next month, an official said, "We are still working through the details and will have more to say (in the future)…It is not clear. The community remains a little confused. The transmittal suggests over the month, but other CMS communications suggest otherwise. We will question CMS about that."

Asked if a 25% reduction in Epogen/Aranesp is realistic, a physician said, "That is what the KDOQI guidelines suggest. The entire community made a recommendation on what is appropriate…and CMS has largely followed the recommendations of the community. There is a little lack of clarity on some issues…and the community as a whole will address these with CMS…It is not atypical that CMS issues clarifications…My belief is doctors will continue to do exactly what they are doing – keep patients in the 11-12 range, but knowing if they exceed 12 or go to 13 that they are still okay."

Reaction to this change included:

- *CMS official:* "This is a loosening of the EPO rules. Many contractors were not enforcing the 90-day rolling hematocrit rule. The new policy simplifies it, so contractors can enforce it."
- "The new guidelines are pretty generous."
- *Amgen official #1:* "We think it is terrific that the policy recognizes the way physicians respond to hemoglobin."

- "A 25% reduction is better than a cap."
- *Amgen official #2:* "We are very pleased with the recent outcome for CMS."

Pay-for-Performance (P4P), also known as Value-Based Purchasing (VBP). P4P has been described as "a tsunami building offshore in a sea of stakeholder unrest, threatening those who are not prepared." VBP and P4P are not exactly the same, but the terms are used interchangeably. An official with the American College of Physicians said, "My personal opinion is we don't know (if P4P will work). It is much too early. We need much more data. I think we are spending too much time on P4P and not enough time on overall quality improvement in healthcare…The kind of patients you (nephrologists) take care of require much more care than they are getting right now…The current payment system is not tenable if we are going to care for these patients over time…It is an open question whether P4P will really lead to quality improvement."

Examples of P4P/VBP programs include:

- **Bridges to excellence.** This is expanding and was described as relatively successful. An expert predicted, "I think this will stay around as a model."
- **Care Focused Purchasing.** This VBP is a group of ~28 very large employers who want to gather large amounts of data on the quality of healthcare provided. A speaker said, "The physician community is wary of this effort because of an intense effort to acquire data on physician performance."
- **Integrated Healthcare Association.** This California P4P effort was described as "relatively successful."
- **CMS pilots.** In nephrology these include:
  - ESRD Disease management demonstration – by Davita and Fresinius. This program, which starts January 1, 2006, is like a Medicare Advantage plan with a monthly cap for all services (ESRD and hospital), and the companies are in charge of managing the care and caring for the beneficiaries.
  - Disease management for Severely Chronically Ill Medicare Beneficiaries.
  - Care Management for High Cost Beneficiaries.
  - Section 623E MMA expanded bundling demonstration.
- **Hospital Quality Initiative.**

Congress and VBP. Medicare Payment Advisory Committee (MedPAC) recommended earlier this year that Congress institute VBP, and House bill HR-3617 was introduced but it does not appear to be going anywhere. Senate bill S-1356 is still possible. A CMS official said, "There is an art and a science to this…As a payor what is important to me is what the outcome is. What is important to practitioners is the process. Early in the program I expect almost all the measures will be process-based because we don't know how to do outcomes well yet, but longer-term there will need to be (outcome improvements)."

Daily nocturnal dialysis. A CMS official said, "I am the project officer on the daily nocturnal dialysis project…The statute and regulations are supportive of home therapies. Right now, payment is three treatments a week, and a fourth where there is medical necessity. In the NIH trial we are sponsoring, we are paying for a fourth treatment for all patients. I am a big supporter of home therapy. The evidence is not compelling enough yet for CMS to make a decision. We are getting some data back from the NIH trial, but as soon as we have the data, I expect we will move forward – not only because it is better but also because it is likely to be a cost saver." Another CMS official, asked about the prospects for a daily dialysis demonstration, said, "I'm a proponent…but there isn't a large enough study to say what it does and what it costs."

MISCELLANEOUS

NABI BIOPHARMACEUTICALS' StaphVax

In early November 2005, Nabi announced that a placebo-controlled, randomized, double-blind, 3,447-patient Phase III confirmatory trial failed to show that StaphVax prevents *S. aureus* infections in dialysis patients. Further clinical trials were put on hold, and the European marketing application was withdrawn. The details were presented at ASN, and the data looked so bleak that sources do not believe there is any hope for this agent.

The primary endpoint curves, when graphed, loooked very similar. Asked why the trial failed, a Nabi official said, "It's hard to know if there were subtle differences in the vaccine from the previous study or if there was a difference in the patient identification."

An analysis of a dataset of 1,804-dialysis patients from the Phase III Study 1356 was also presented. Researchers concluded, "StaphVax significantly decreases the incidence

P4P vs. VBP

	Pay-for-performance	Value-based purchasing
Theory	Links pay to a measure of individual, group, or organization performance. Incentivizes physicians to do a better job	Buyers should hold providers of healthcare accountable for both cost and quality of care
Early experience	Few studies, but recently published study found mixed results and that physicians with baseline performance at or above the performance threshold for receipt of a bonus improved the least but received the largest share of the bonus payments	N/A

of first-time and recurrent *S. aureus* bacteremia in hemodialysis patients. We hypothesize that this may be related to facilitated opsonophagocytosis, due to persistent high levels of anti-*S. aureus* type-specific CPS antibodies or, alternatively, a direct effect on bacteria colonizing the dialysis access device or bacteria."

♦

Study 1356 Subset Analysis in Dialysis Patients

Variable	Hazard ratio	p-value
Risk factors for *S. aureus* bacteremia		
Nasal carriage	1.65	0.03
Age ≥45 vs. <45	1.9	0.05
Diabetes	1.94	0.003
Prior access infection	2.48	0.0002
Graft vs. fistula	2.49	0.002
Risk factors for recurrent *S. aureus* bacteremia		
StaphVax/placebo	0.67	0.04
Diabetics	1.49	0.06
Mean days to recurrent *S. aureus* bacteremia	171.8 days	120.4 days
Distribution of *S. aureus* bacteremia		
Frequency of *S. aureus* bacteremia	**StaphVax**	**Placebo**
1	5.38%	4.14%
>1	38.78%	21.62%

StaphVax Phase III Safety

Measurement	StaphVax		Placebo	
	Any	Severe	Any	Severe
Local				
Ache	16.7%	0.7%	6.6%	0.4%
Burning	4.7%	0	2.0%	0
Heat	7.5%	0.2%	3.6%	0.1%
Swelling/induration	10.9%	0.6%	5.0%	0.2%
Redness	9.9%	0.5%	4.7%	0.1%
Tenderness	19.9%	0.5%	5.1%	0.1%
Systemic				
Fever	6.2%	0.2%	5.9%	0.1%
General discomfort/malaise	16.9%	1.0%	11.5%	1.0%
Headache	14.8%	1.0%	15.8%	1.2%
Muscle aches/myalgia	17.5%	0.7%	11.2%	0.6%
Nausea	9.2%	0.6%	9.4%	0.6%
Vomiting	3.8%	0.3%	4.2%	0.6%

StaphVax Phase III Infections

Measurement	StaphVax 1.0 mL n=1,673	Placebo n=1,686
Staph aureus infections		
Total microbiologcially confirmed	140 patients	137 patients
All first episode bacteremia	69	61
First episode bacteremia Weeks 1-2	4	0
First episode bacteremia Weeks 3-35	45 of 45	37 of 37
Serotype 336 (non-vaccine)	16%	16%
Vaccine-type	84%	84%
All in-vaccine cases Weeks 3-35	85 patients	81 patients
Vaccine-type invasive cases Weeks 3-35	74 patients	70 patients
Infection characteristics		
Bacteremia without documented local infection	74%	74%
Bacteremia with cellulitis/soft tissue abscess	10%	10%
Bacteremia with osteomyelitis	0	3%
Bacteremia with septic arthritis	0	3%
Bacteremia with UTI	3%	3%
Bacteremia with other	13%	6%

StaphVax Phase III Efficacy

Measurement	StaphVax 1.0 mL n=1,673	Placebo n=1,686	Efficacy
Primary endpoint: Vaccine-type *S. aureus* bacteremia Weeks 3-35	38 patients	31 patients	-23.1% (Nss)
Secondary endpoint #1: Vaccine-type *S. aureus* bacteremia Weeks 3-28	33 patients	26 patients	-27.5% (Nss)
Secondary endpoint #2: All vaccine-type *S. aureus* infections Weeks 3-35	74 patients	70 patients	-6.4% (Nss)
Secondary endpoint #3: All serotypes *S. aureus* bacteremia Weeks 3-35	45 patients	37 patients	-21.6% (Nss)
Secondary endpoint #4: Vaccine-type *S. aureus* bacteremia Weeks 3-54	52 patients	46 patients	-13.0% (Nss)