Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Use of Amgen's Epogen and Aranesp is likely to decrease due to the CHOIR trial, which found that hemoglobin >13 increased the risk of heart attack, death, and stroke. Doctors plan to more closely target Hgb 11-12, CMS is expected to reinstitute a hemoglobin ceiling for reimbursement, and the KDOQI anemia guidelines may change.

♦ Nephrologists were very excited about Roche's once- or twice-monthly Mircera, which increases hemoglobin more gradually and perhaps makes it easier for doctors to manage hemoglobin levels. ♦ Advanced Magnetics' ferumoxytol, an IV iron in development that requires fewer injections than current products, appears efficacious, but the safety data were not fully presented, and nephrologists expressed little excitement over it, so some questions remain.

♦ AffyMax's hematide continues to look promising, not only as a new, non-refrigerated, and perhaps less expensive ESA, but also as a treatment for PRCA.

♦ Phase II data on Keryx BioPharmaceuticals' new phosphate binder looked promising. Nephrologists generally were unaware of it but interested in a new product.

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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

AMERICAN SOCIETY OF NEPHROLOGY'S RENAL WEEK

San Diego, CA
November 16-19, 2006

Renal Week, the American Society of Nephrology (ASN) annual meeting, was dominated by discussions of the correct hemoglobin levels to target in chronic kidney disease (CKD) and dialysis patients, but there were new data on new anemia treatments, particularly Roche's Mircera (CERA), as well as data on a promising new intravenous iron from Advanced Magnetics and a new phosphate binder in development by Keryx BioPharmaceuticals.

OUTLOOK FOR ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)

It appears likely that use of ESAs will go down as a result of the CHOIR and CREATE trials. There has been general agreement that hemoglobin <11 is not good, but now hemoglobin >12 may not be good for CKD patients either.

CHOIR, which was published in the ***New England Journal of Medicine*** on the first day of the ASN meeting, studied 1,432 patients with CKD (pre-dialysis) treated with Johnson & Johnson's Procrit (epoetin alfa) to boost levels of hemoglobin in the blood. Half the patients were treated with a hemoglobin goal of 13.5, and the other with a target of 11.3 g/dL. This open-label study sponsored by

16-Month CHOIR Trial Results

Measurement	HIGH Target Hgb 13.5 n=715	LOW Target Hgb 11.3 n=717	p-value
Completed 36 months	312	49	---
Withdrew prior to study early termination	278 patients	271 patients	---
Smokers	40%-50%	40%-50%	---
Mean hemoglobin achieved	12.6 g/dL	11.3 g/dL	---
Primary events	125	97	---
IV iron required	52%	48%	---
MI	18 patients	20 patients	---
Primary endpoint: Composite of death, MI, stroke, and CHF hospitalization	1.34 HR for higher risk (125 events)	--- (97 events)	0.03
Deaths	1.48 HR for higher risk with HIGH		0.07
CHF hospitalization	1.41 HR for higher risk with HIGH		0.07
Stroke	1.01 HR for comparable risk		0.98
MI	0.92 HR for comparable risk		0.78
First cardiac event	19.2%	15.5%	---
Quality of life by LASA, KDQ, and SF-36	Improved	Improved	Nss
Emotional component of SF-36	---	Significantly higher	---

J&J, was stopped early in May 2005 by the data safety monitoring board because of an excess of cardiovascular adverse events. Researchers found that patients with the higher hemoglobin target had a 33.7% increased risk of death, MI, stroke, and their "strong recommendation was to target hemoglobin (Hgb) of 11-12 in all CKD patients."

CREATE was an international trial of 603 patients with Stage 3-4 CKD and mild-to-moderate anemia (hemoglobin 11-12.5 g/dL) who were given Roche's NeoRecormon (epoetin beta). In one arm, the hemoglobin target was 13-15 g/dL, and in the other arm the target was 10.5-11.5 g/dL. Investigators found that the higher hemoglobin target did not reduce cardiovascular events (the primary endpoint) or all-cause mortality, but the time to dialysis and quality of life were significantly shorter in the higher target hemoglobin arm. The risk of congestive heart failure (CHF) also was higher in the higher target hemoglobin arm. At Year 1, quality of life was better in the high-target group, and this benefit was maintained out to Year 2. An investigator said, "CREATE supports the current guidelines. It does not endorse routing Hgb normalization."

CREATE Trial Results

Measurement	High Hgb 13-15 g/dL n=301	Low Hgb 10.5-11.5 g/dL n=302
First cardiovascular event in pre-dialysis patients	34	39
First cardiovascular event in dialysis patients	24	8

Korean trial. A small, multicenter, prospective, randomized study from Korea also evaluated the long-term efficacy and renal outcome of recombinant human erythropoietin (rhuEPO) in pre-dialysis patients followed for two years, and this study suggested that the correction of anemia in CKD may ***accelerate*** renal deterioration. Even adjusting for the effect of diabetes, the researcher said the EPO-treated patients reached the composite endpoint – a doubling of creatinine, initiation of dialysis, or death – earlier than the patients in the control group.

2-Year Results of rhuEPO in Pre-Dialysis Patients

Measurement	Control n=43	rhuEPO SC n=60	p-value
Primary endpoint: Composite of creatinine doubling, initiation of dialysis, or death	N/A	***Significant increase:*** more creatinine doubling, more dialysis, and reached endpoint earlier than control	<.05
Mean blood pressure	94.5	98.5 (Nss)	Nss
Hemoglobin	8.64 g/dL	10.48 g/dL	<.001

FDA. Currently, the hemoglobin levels recommended by the FDA are:

- 11-12 g/dL for Amgen's Epogen (epoetin alfa).
- 10-12 g/dL for J&J's Procrit.
- 11-12 g/dL for Amgen's Aranesp (darbepoetin alfa).

On November 16, 2006, the FDA issued a public advisory on the use of ESAs in CKD patients. The Agency warned that "a newly published clinical study (showed) that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL…The CHOIR study findings underscored the importance of following the currently approved prescribing information for Procrit, Epogen, and Aranesp, including the dosing recommendation that the target hemoglobin not exceed 12 g/dL."

An Amgen official said, "Amgen is very supportive of FDA efforts to continue to reinforce the hemoglobin 10-12 target, and Amgen is working to share this public advisory with customers."

CMS. The Centers for Medicaid and Medicare (CMS) currently reimburses for hemoglobin >11 g/dL, with no upper limit or cap. Sources generally agreed that CHOIR will cause CMS to reinstitute a cap on ESA reimbursement, probably at 12 g/dL.

A University of Wisconsin pharmacist and CMS consultant who presented a CMS poster said, "It is a very real possibility that reimbursement could be lowered if CMS determined the findings are real. The upper limit cap (on ESA reimbursement) was taken off because the community convinced the agency that there was no reason for a cap, but this (CHOIR) could lead to putting it back on…There was always a suggestion of risk with (high) hemoglobin. There has been tremendous enthusiasm for a high hemoglobin, but this (the CHOIR results) will really grab attention…CHOIR is a different population (pre-dialysis), but it would be foolish to say the results would be different in dialysis…CHOIR has huge implications for patient care as well as reimbursement."

He suggested three ***possible*** reasons that a high hemoglobin target might increase mortality:

1. The need to give more iron to get to a higher hemoglobin.
2. A change in blood flow as the blood becomes more viscous with a higher hemoglobin.
3. Subgroups that are more at risk (e.g., diabetics).

An Amgen official commented, "We don't know how they will react or if there will be any changes…We don't expect any big change." A doctor said, "I don't think the (guidelines) will change. We should still shoot for 11-12."

U.S. Congress. Shortly after ASN, the Government Accountability Office (GAO) recommended that Medicare bundle

anemia drugs with overall payments for dialysis services to improve efficiency and contain costs, rather than paying for the drugs separately as is currently done. The House Ways and Means Committee also held a hearing to discuss use of ESAs and increasing Medicare spending for them.

However, EPO reimbursement is not the only topic the new Congress is likely to consider. An ASN official said, "Clearly, there will be some changes with the new Congress, probably including a consideration of changes in how Medicare Part D is structured. And it is likely that Congress will attempt to negotiate drug prices for Part D. I hope the new Congress will increase immunosuppressant coverage for kidney transplant patients for life."

KDOQI guidelines. The National Kidney Foundation, which issues the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines on anemia treatment, recommends treatment to a hemoglobin goal of 11 g/dL and expresses caution for levels above 13 g/dL. Sources speculated that the guidelines, which were just updated earlier this year, may have to be updated again in light of CHOIR.

Physicians. Doctors at the meeting indicated they will become more conservative in Epogen use, lowering doses when patients go even a little over a hemoglobin level of 12. Keeping patients in a tight 11-12 g/dL range will be difficult, doctors said, but that is what they insisted they will be targeting.

A former president of ASN predicted there would be "at least an asterisk (change)" to the guidelines post-CHOIR. He also predicted that CMS would modify reimbursement and probably impose a cap on ESA use. However, he believes it will take time before doctors change their ESA use, "It (CHOIR) will be a topic of conversation, but it will take time (to change what doctors do). People will wait for expert groups, though those at the higher end (of hemoglobin) might become more conservative."

Asked if the CHOIR trial is convincing, he said, "A rock has been turned over in what to do for dialysis patients. There will be a lot of discussion of that."

Asked if there is a consensus that you shouldn't go to a hemoglobin <11, he said, "Yes, but there is no scientific (mortality) evidence."

The chairman of the ASN's Public Policy Board said it is ***possible*** the KDOQI anemia guidelines will be revised again as a result of CHOIR, but he added, "When science becomes available, I think it is likely there will be a re-thinking and reforming of group targets…CHOIR is brand new data. The population (pre-dialysis patients) is not a dialysis population but the results will be looked at in the context of other randomized clinical trials…The concern is being too restrictive based on one study…I'm sure people will scrutinize the data, and based on that target hemoglobin may change. They may extrapolate (CHOIR) to dialysis patients, but that needs to be carefully analyzed…I suspect that CKD patients at a minimum will be carefully scrutinized, and there may be enough available information to change the guidelines." He said CHOIR will not change his personal practice, which is to target hemoglobin at 11-12 g/dL.

Asked what evidence is needed to change the KDOQI guidelines, he said, "Any time there is a large, high quality study with new information that is different from available information, it is time to consider whether the guidelines should be reviewed. And this may lead to reconsideration of practice guidelines."

Other comments included:

- "It is very difficult to (keep patients between Hgb 11-12, even with frequent dosing of Epogen three times a week in dialysis patients…It is really difficult to get Hgb stabilized in the 11-12 range even in relatively stable patients …It would be really tough if I had to stick to a 1 g/dL range."
- "We do the best we can in the recommended ranges, but there are many, many variables that can alter our best intentions."
- "I will change what I do. It's not that I target >12 g/dL, but I haven't worried if patients go >12. Now, I'm a little more nervous about high hemoglobin…The government, the networks, and the (dialysis) companies are after you to keep patients >11 g/dL, and I get a bonus from Fresenius based on having all my patients over 11. To do that means I end up with some patients 13+…It is difficult to keep patients between 11 and 12 g/dL. If the bottom is 11, then the top is usually 14, and patients don't feel bad over 13…If CMS imposes a cap, a lot of patients will go below 11 g/dL."
- *CHOIR investigator:* "I don't think the data should cause a knee-jerk reaction. We don't want to frighten doctors about the science of applying these findings to patients, and right now, what I hear is fear."
- *North Carolina:* "A year ago, if a patient's hemoglobin was 12.4, I would let it ride. Now, I'll cut the dose until the patient is consistently <12."
- *U.K.:* "I think we should be more careful (with Hgb targets). Leaving people a little anemic is better than going too high."
- *California #1:* "After CHOIR, we'll bring patients down faster and be more rapidly responsive."
- *California #2:* "My current hemoglobin target is 11-12.5. After CHOIR, I won't shoot for 13; I will cut that down."

Dialysis centers

Sources generally agreed that DaVita and Dialysis Clinic Inc. (DCI), the two largest dialysis providers in the U.S., are fairly

comparable. DaVita has had a reputation for being aggressive in anemia treatment, and a paper presented at ASN reported that 37% of DaVita patients had Hgb levels >14 at least once in a 9-month period, but doctors generally defended DaVita's use of ESAs.

Physician comments about dialysis providers included:

- *California:* "I think DaVita is the best dialysis provider. They focus not on quality outcomes but on patients. They are not driven by the bottom line as much (as other dialysis providers)…(But) we did move more patients out of <11 g/dL, and so more of our patients hit 13 g/dL."
- *Georgia:* "My impression is that DaVita is computerized much better (than competitors). Fresenius is trying to get computerized. They keep saying, 'It's coming. It's coming'…NRA (National Renal Alliance) is rolling one (computerized system) out…Fresenius sometimes is difficult to get along with. It's tough to get them to approve research projects. Fresenius also looks at guidelines almost to a fault, but they've always wanted hemoglobin between 11 and 12."

Testifying before a congressional committee, Dr. Anjay Singh of Brigham & Women's Hospital, a principal investigator in CHOIR, said, "The United States Renal Data System (USRDS), a large federally funded registry of patients on dialysis, in its 2006 report indicates that more than 40% of dialysis patients have a hemoglobin level >12 g/dL. Over 20% have hemoglobin levels >13 g/dL. The explanations provided for this include the inability to target a narrow range of hemoglobin because of a phenomenon termed hemoglobin cycling and that patients have excursions in hemoglobin levels beyond the 12 g/dL range for only a very brief period of time. However, achieving the FDA recommended range is achievable by some dialysis chains. Only 30% of patients dialyzed at DaVita facilities have hemoglobin levels of <12 g/dL, whereas over 80% of DCI patients are able to maintain their hemoglobin level at <12 g/dL. As well, USRDS data suggest that excursions over 12 g/dL may occur for 3 or more months. The strategy of targeting patients using higher epoetin doses to a higher hemoglobin with these transient excursions could be harmful."

However, DaVita also reportedly has shown a lower mortality rate than some other centers. A Midwest nephrologist said, "If mortality really is lower, it could be in spite of higher hemoglobin, not because of it."

Dr. Stephen Fadem of the University of California, San Diego, a DaVita medical director, defended dialysis center use of ESAs, saying, "This is not Lupron (where TAP Pharmaceuticals paid more than half a billion dollars to settle a Medicare fraud case). EPO has had a tremendously positive impact...I never prescribe EPO to make money for DaVita or any company…After CHOIR, I won't strive for 13.5; I will target 11-12 – because now there is scientific evidence that is the best target range…DaVita does not tell me how to practice medicine. I write the orders, approve the protocol, and supervise it. And then I wander around (the center) to be sure the protocol is followed."

The furor at Renal Week

➢ **Late-breaker.** ASN organized a special late-breaking session at which the principal investigators of both CHOIR and the CREATE trials presented their findings and answered questions from doctors in the audience. Even though this was a hot topic at the meeting, the late-breaking session was sparsely attended.

➢ **Debate.** A Roche-sponsored lunch was devoted entirely to a debate on the KDOQI guidelines, with no mention of CERA at all. Before the debate, 64% of doctors in the audience said they agreed with the current KDOQI anemia guidelines, which most recognized (correctly) as ≥11 g/dL, and after the debate 69% agreed with the current KDOQI guidelines.

Raising the hemoglobin limit from 12 to 13 g/dL is good for patients

Dr. Allen Nissenson of UCLA argued that there is overwhelming evidence that Hgb <11 is associated with adverse clinical outcomes, and overwhelming evidence that as hemoglobin rises above 11, quality of life improves. He argued that it is essential for all patients to have a Hgb >11, but moving the upper limit to 13 may increase the number of patients who transiently exceed 13 but will not increase the number of patients maintained >13. He also contended that there is no evidence that maintaining Hgb >13 is beneficial, except for improving quality of life, so the decision whether to target closer to 11 to minimize risk or to target 13 to maximize the benefits "is a decision that needs to be individualized for each patient."

Among the points Dr. Nissenson made were:

- "Although quality of life improves when hemoglobin is >13, the risks also go up…and that statement is not meant to apply to patients when the hemoglobin level transiently exceeds 13."
- The ***risks*** of raising the hemoglobin limit to 13 include an increase in cerebrovascular events (stroke).
- The ***benefits*** of raising hemoglobin to >13 include:
  - Improved quality of life, fewer hospitalizations, lower cost, and improved mortality. He said, "I urge you to look at the quality of life data. There are overwhelming data…Over 20 RCTs show progressive improvement in quality of life with a hemoglobin increase from 9 to 12."
  - The DaVita database looked at all-cause death in 60,000 patients…and the sweet-spot with the lowest mortality is hemoglobin 12-13 – after adjustment for case mix and inflammation.
  - Patients with the highest hemoglobin levels have the lowest healthcare costs.

- From chemotherapy data, it is clear the higher the hemoglobin, even up to 39, the lower the mortality, and the lower the hospitalization rate.
- The newly-published guidelines for the Royal College of Physicians in the U.K. recommends an Hgb of 10.5-12.5. He said, "Maybe that would be a more common group. By having an upper limit of 13, we are likely to achieve this level."

The case against a higher hemoglobin limit

Dr. Daniel Coyne of Washington University argued this side of the issue, suggesting targeting higher hemoglobin levels is done more for the profits of the manufacturers and dialysis centers than to benefit patients. He said, "Most of you probably think normal Hgb is best for patients…But who taught you that?...And what were their motivations for doing that? Dialysis mortality rates have not changed over the last 13 years. In 2005, ~50% of dialysis patients had Hgb ≥12. Being above target is not considered bad. But profits increase for both ESA sellers and most buyers when use increases. Is the target too narrow or is the goal to be as high as possible and maximize profits?...Treating patients to targets >13 may increase the risk of serious adverse events...We have to demonstrate a way to get to a higher hemoglobin safely before we recommend it."

Dr. Coyne cited several studies that normalization of hemoglobin or high hemoglobin is not beneficial, so higher guidelines have not been justified, "When you go through the evidence tables looking at quality of life, the KDOQI committee is assuming or implying that small hemoglobin changes actually improve quality of life and are clinically significant (in dialysis patients), but that is not scientifically valid. And the data in CKD patients are even weaker…Is there sufficient evidence that a Hgb limit of 13 is as safe as a limit of 12? No. And if you do shoot for a higher hemoglobin and have an adverse event, I suggest you learn to tell the patient's wife you were trying to increase their quality of life insignificantly during the adverse event."

Other points he made included:

- Patients should be told that improved quality of life comes at a price (possible harm).
- There are no randomized data showing quality of life improves significantly when a hemoglobin level of 12 is targeted instead of 11.

➢ **ASN press conference.** ASN officials held a press conference to discuss the controversy over hemoglobin levels.

Asked why the medical society has left development of guidelines to the National Kidney Foundation (NKF), an ASN official said, "I wouldn't say that we left that to the National Kidney Foundation. Rather, I'd say that (guidelines) is something the National Kidney Foundation chose to do, which is more in keeping with their mission…It was not something we thought appropriate for ASN…And they have been involved in the guidelines for many years…We have been primarily concerned with other issues." Dr. William Heinrich, ASN president-elect, added, "The ASN has focused primarily on educational meetings, dissemination of information, and promulgation of literature across meetings…It is not that we couldn't develop guidelines, but a sister society has done so and done so well…They produced them with such zeal that we basically allowed or encouraged them to do it."

Asked if they have any issues with the NKF guidelines, an ASN official said, "We have not systemically evaluated the guidelines to seek an up or down vote on them…It is important to recognize that the guidelines were developed by outstanding clinicians and experts in the field, and they involve both evidence-based and opinion-based information …And the process is quite extensive and difficult. ASN, as an organization, did not decide to go down that road."

Asked if industry has had an undue influence on the guidelines, an ASN official said, "You talk about guidelines that don't have anything to do with this organization…I don't have any knowledge of any influence whatsoever." Dr. Heinrich added, "The way the guidelines are written, there are several very distinct rules which are meant to keep any undue influence away from the guidelines." A CHOIR investigator added, "The KDOQI guidelines are a recommendation, not a rule. Applying conspiratorial theories to how the guidelines were designed is wrong." However, he believes the guidelines absolutely should be re-opened (revised) in light of the CHOIR results.

Asked if he is comfortable with a hemoglobin 13 limit or whether the guidelines need to be revisited, the ASN official said, "Based on the studies reviewed (here), it would be prudent for our members and for us to emphasize that the labeling, the packaging, and the FDA are all consistent, suggesting it be 11-12 and no more until more is known."

Asked if the CHOIR and CREATE results can be applied to dialysis patients since those trials were in CKD, not dialysis, patients, Dr. Singh said, "Strictly speaking, the dialysis population and pre-dialysis patients are different populations. We don't understand precisely what the differences are...but we understand there are differences…but the guidelines don't differ in hemoglobin goals…While we agree there is a difference in the two populations, the guidelines committee has not chosen to distinguish between the two, and the FDA has not chosen to precisely distinguish between them."

Asked if it is possible that the ESA dose is the problem (e.g., if patients need – and are given – a lot of ESA to get hemoglobin up just a little), Dr. Singh said, "This (CHOIR) study was not designed to test the efficacy of the Epogen dose… (But) there is a lot of debate on whether this could be a hemoglobin or an EPO effect…EPO could play a role, but we just don't know that yet…It would be irresponsible to state that we think one or the other…There really isn't evidence to support one thesis or another…We need more studies."

Asked if he will be more conservative about how much Epogen he gives going forward, Dr. Jonathan Himmelfarb of Maine, Chairman of the ASN's Public Policy Board, said, "I agree that the appropriate hemoglobin target is 11-12…In terms of variability around the target, in clinical practice the use of EPO doesn't allow you to titrate extremely precisely…The real question is: In targeting 11-12 would a practitioner be a little less comfortable if hemoglobin drifts higher? Personally, I would say yes."

Asked if overshooting the hemoglobin target could be minimized by use of longer-acting drugs (e.g., Roche's Mircera), a French researcher said, "Given the large biovariability and different responses of patients to EPO, I would not expect that longer-acting agents would solve this problem…They may be of help in patient management, with fewer injections, but variability between patients would be so high…that I don't see this bringing an advantage…Probably what is most important is patients being followed as closely as possible."

ESAs on the Market or in Development

AffyMax's hematide

Nephrologists are keeping an eye on this drug, and those questioned described it as promising – both as a new ESA and potentially as a treatment for pure red blood cell anemia (PRCA). A doctor suggested hematide may not have to be refrigerated and may be cheaper than the other ESAs available.

Data from a Phase II trial in 74 ESA-naïve patients were presented at ASN, and the results looked good. Dr. Iain Macdougall of King's College Hospital, U.K., called the results "very promising," noting:

- Multiple monthly SC and IV injections were well tolerated.
- Correction of anemia (Hgb ≥11) was achieved by Week 8 in 93% of patients on the 0.05 mg/kg dose and by 10% of patients on the 0.075 mg/kg dose.
- Ferritin was maintained "fairly well" in all cohorts.

Hematide Phase II Results

Measurement	Hematide Q4W 0.025 mg/kg SC n=15	Hematide Q4W 0.050 mg/kg SC n=29	Hematide Q4W 0.075 mg/kg SC n=15	Hematide Q4W 0.050 mg/kg IV n=15
Baseline hemoglobin	10.2 g/dL	10.3 g/dL	10.2 g/dL	10.0 g/dL
Patients requiring a dose increase	40%	10%	0	7%
Patients requiring a dose decrease	7%	34%	33%	33%
Adverse events	63% reported a total of 185 events			
Drug-related adverse events	11 patients: 8 hypertension, 2 arrhythmia, 1 headache, 1 malaise, 1 insomnia, 1 fluid overload			
Serious adverse events	12 events, not drug related: gastritis, diabetic ketoacidosis, vomiting, hematoma, peritonitis, ankle fracture, cellulitis			
Antibodies	1 patient with low level antibodies, reported doing well with Hgb maintained at 11-12. No PRCA.			

So far, about 300 patients have been treated with hematide, including some PRCA patients. Hematide may treat – but not prevent – PRCA. A Stanford researcher presented a rat study which found that hematide can treat PRCA. PRCA was induced in 20 rats: 5 controls, 6 given an IV injection of 0.5 mg/kg hematide which increased hemoglobin to 10, and this hemoglobin was maintained with hematide injections every 50-60 days for a year. Another 6 rats were given a single injection of 1.0 mg/kg hematide, which increased hemoglobin to 19, an effect that lasted out to 80 days and then was maintained with injections every 2-3 months. The investigator said, "The data clearly show…this peptide has the potential to treat anemia in CKD patients with confirmed antibody-mediated PRCA." She said the drug did not show any immunogenicity in this study.

Only the once-monthly 0.05 mg/kg SC and 0.05 mg/kg IV doses are going forward in a large (several hundred patients) Phase III trial which is expected to start in 1H07.

Amgen's Epogen and Aranesp (darbepoetin alfa)

Amgen officials emphasized that Amgen is considered by nephrologists as "a leader in nephrology," and they pointed out that Fresenius recently signed a long-term (5-year) contract for Epogen. Officials made several interesting points about Epogen and Aranesp use:

- The underlying ESA demand in free-standing dialysis centers is consistent with an annual ESRD patient population growth of 3%-4%.
- At any given point, 45%-50% of dialysis patients have hemoglobin >12.
- Amgen has 61% market share in nephrology clinics.
- Only about 50% of CKD patients who could be treated for anemia are being treated. About 2.2 million CKD patients are under the care of a primary care physician, and that market is only about 5%-6% penetrated.
- Doctors may try to target a narrow hemoglobin range – between 11 and 12 – but, because of patient variability, patients frequently overshoot that. Within 3 months, 84% of patients >12 are back down <12.
- CRP is strongly predictive of hemoglobin level and EPO dose requirements. Patients with the highest CRP (>30 mg/L) have the lowest hemoglobin, and patients with low CRP (<15), need a lower EPO dose. Reportedly, about 28% of patients have CRP >30 (which is common in the CKD population), 38% have CRP ≤30, and 32% have CRP <15.

- Conversion from Epogen to Aranesp in dialysis patients stabilized in mid-2006 at ~$200-$240 million.
- The impact from reimbursement changes (to ASP + 6%) has been minimal so far.
- Amgen is in discussion with the FDA over the company's application for approval of Aranesp in pre-dialysis patients. Apparently, the FDA had some "minor" questions, and Amgen planned to talk with the FDA to see if current data address the questions or if a new clinical study will be needed.

Ongoing trials include:

1. TREAT, which is seeking to prove that treatment with Aranesp reduces the risk of mortality and non-fatal cardiovascular events in CKD and Type 2 diabetics. This 4,000-patient trial, comparing Hgb 13 to Hgb <9, is >70% enrolled. The primary endpoint is all-cause mortality. An expert said, "We already know <9 is not good, so if TREAT finds 13 is better than 9, it won't tell us much."

Many nephrologists were concerned about whether TREAT should be allowed to continue. A nephrologist asked an expert: "I'm troubled by the comment that TREAT should go ahead with two huge U.S. studies showing serious adverse events. I'm not comfortable randomizing to high hemoglobin. Would you enroll patients? Should TREAT go on?" The expert response, "TREAT has a DSMB, and they have this (CHOIR and CREATE) information, and I think as long as they do that, it can continue." An Amgen official said, "TREAT is more than 70% enrolled. The DSMB met (recently) and recommended it continue without change."

Asked what TREAT is expected to prove, an Amgen official said, "That anemia treatment can improve cardiovascular outcomes and overall survival. Currently, there are uncertainties (about this). TREAT is expecting a 12.5% placebo effect (on survival) and a 20% treatment effect."

2. RED-HF, which is testing Aranesp in 1,700 patients with symptomatic left ventricular systolic dysfunction and anemia to see if it decreases the risk for all-cause mortality or hospital admission for worsening heart failure.

Asked if there are any plans to change the hemoglobin targets in these trials given the recent FDA advisory on hemoglobin targets, an Amgen official said, "Not at this time. TREAT has been ongoing since August 2004 and is more than 70% enrolled…It has been reviewed by an independent DSMB, which meets quarterly…Last week there was a DSMB meeting, and all CHOIR and CREATE data were reviewed… and the recommendation was that TREAT should continue as designed, with no change to target hemoglobin…The DSMB also recognized the possibility that people may read a lot into the publications (of CHOIR and CREATE), and it is important to say that they read all the data, and the TREAT trial should continue forward because the question it is answering is more important than ever."

Cost. A U.K. study compared epoetin beta (e.g., NeoRecormon) and Aranesp. The researchers concluded that the products are comparable in efficacy in dialysis patients, "It is our opinion that the choice should be determined by cost." They found the potential annual savings of using only subcutaneous EPO would be $349,544-$404,456.

Cost Comparison of EPO and Aranesp

Measurement	Number of patients	Dose	Mean Hgb	Weekly cost	Potential weekly excess cost over EPO SC
EPO subcutaneous	119	7941 IU	11.4 g/dL	$115.68	---
EPO IV	65	9200 IU	11.4 g/dL	$134.02	$7,391
Aranesp subcutaneous	39	45.4 µg	11.7 g/dL	$132.36	$6,722
Aranesp IV	180	46.3 µg	11.7 g/dL	$134.97	$7,778

FIBROGEN

The company held a poster reception to provide an opportunity to talk with officials and researchers.

➢ **FG-2216.** This is the company's lead anemia candidate. It is an oral small molecule inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) which works by stabilizing HIF and thereby promoting endogenous production of erythropoietin. FG-2216 does not act on the EPO receptor directly. Phase II data in CKD (pre-dialysis) are expected at ASN 2007, and a Phase II trial in dialysis patients is due to start in 2007.

➢ **FG-4539.** This second-generation oral anemia compound is more potent that FG-2216. It is being developed first in ischemia and is going into humans "soon," in normals first. An official said the immediate goal is to start a Phase I trial in Europe by the end of this year, looking at safety and PK. Then, a Phase II trial is expected in stroke.

➢ **FG-3019 (CTGF).** Data from an uncontrolled, open-label, multicenter, uncontrolled, dose-escalation Phase Ib trial in microalbuminuria were presented at ASN. The trial tested two IV doses – 3 mg/kg and 10 mg/kg – over an 8-week treatment period, with follow-up to Day 365, in Type 1 and Type 2 diabetics with microalbuminuria, and there was little difference between the two doses. Researchers concluded, FG-3019 was well tolerated and decreased ACR at both doses.

An official said the Phase Ib FG-3019 results support starting a Phase II in macroalbuminuria (diabetic nephropathy) in 2007, with glomerular filtration rate (GFR) and cardiovascular endpoints. Then, the company plans to test for survival in Phase III. The doses for this trial will be 1 mg/kg and 5 mg/kg administered Q2W by infusion. There will be a three-month run-in and a six-month treatment period. The trial is expected to take a year to enroll. The primary endpoint will be ACR,

but visual acuity will also be measured by an ophthalmologist at the beginning and end of the trial. Dr. Lea Sewell, a Fibrogen rheumatologist who is the clinical lead on this project, said the FDA wants to see a 50% reduction or return to normal, "If you do ACR change, then they look at a lot of safety and other things. If GFR is the endpoint, that's okay with the FDA. The FDA doesn't think change in ACR is a very exciting endpoint."

Fibrogen is also researching a SC formulation, but Dr. Sewell said that nephrologists can learn to give infusions the way rheumatologists learned to give Remicade (Johnson & Johnson, infliximab) infusions for rheumatoid arthritis. Getting endocrinologists to do infusions might be more difficult because they don't necessarily have an infusion room.

Phase Ib Trial of FG-3019 (CTGF)

Measurement	3 mg/kg FG-3019 n=14	10 mg/kg FG-3019 n=10
Type 1 diabetics	21%	20%
Type 2 diabetics	79%	80%
PK		
C_{max}	76 µg/mL	511 µg/mL
T_{max}	2.25 hours	6.0 hours
$T_{1/2}$	4.3 days	5.6 days
Drug accumulation	0	Limited
GFR change at Day 56	+3.6%	
Change in systolic BP	-3.6 mmHg	
Change in diastolic BP	-2.1 mmHg	
ACR change from baseline	-19 (p=0.144)	-34 (p=0.102)
Adverse events		
Any	100%	70%
Headache	21%	0
Fatigue	7%	10%
Edema	7%	10%
Skin cut	14%	0
Anemia	7%	10%

ROCHE'S Mircera (CERA, continuous erythropoietin receptor activator)

Most nephrologists questioned were very excited about this potential new ESA with twice monthly, and perhaps monthly, dosing. Mircera has been submitted to the FDA for approval for use in the treatment of anemia associated with CKD (both dialysis and non-dialysis patients), and the PDUFA date was February 20, 2007, but Roche recently announced that it "proactively" provided the FDA with additional data, which will extend the FDA review period by three months.

Data presented at ASN showed that both pre-dialysis CKD patients and dialysis patients can be successfully treated with Mircera, and the increase in hemoglobin was more gradual than with Epogen, which may be another advantage, given the new focus on keeping hemoglobin in the tight 11-12 g/dL range. A Georgia nephrologist said, "There is excitement about it. Amgen has been so aggressive in raising the price of Epogen that I personally would look for any excuse to use a non-Amgen drug. People are looking for choices." A California doctor said, "I like the idea of competition to drive down prices." A European doctor said, "CERA looks like it works very well. I would use it if it were available." Another U.S. doctor added, "If it really has less variability (than Aranesp or Epogen), that will be attractive. Nephrologists are more than willing to switch if they perceive a benefit in terms of less PRCA, better patient outcomes, or a lower price."

There were no podium presentations on CERA, but Roche presented at least eight posters on CERA, including:

1. **ARCTOS – Q2W SC CERA dosing in CKD vs. Aranesp.** This pivotal Phase III trial was a randomized, open-label, multicenter, parallel group study comparing CERA (starting dose 0.60 µg/kg SC every two weeks) and Amgen's Aranesp (starting dose SC 0.45 µg/kg QW) for 28 weeks in 324 patients with CKD who were not on dialysis. The dose of both agents was adjusted to achieve an Hgb increase of ≥1 g ***and*** Hgb ≥11, and then to maintain Hgb within the 11-13 g/dL range. After 28 weeks, patients who responded to Mircera were randomized to continue treatment twice a month or monthly with the same dose, while patients on Aranesp remained on once-weekly treatment.

Researchers concluded twice-monthly CERA:

- Effectively corrects anemia and provides a smooth and steady Hgb increase.
- Leads to significantly fewer patients exceeding the recommended Hgb levels during the first 8 weeks.
- Is safe and well tolerated.

Phase III CERA Results in CKD

Measurement	CERA SC n=162	Aranesp SC n=162
Baseline Hgb	10.22 g/dL	10.15 g/dL
Primary endpoint #1: Hgb increase of ≥1 g ***and*** Hgb ≥11 by ITT analysis	97.5%	96.3%
Primary endpoint #2: Mean Hgb in per-protocol patients	12.33 g/dL	12.17 g/dL
Patients with Hgb >13 at any time	67.7% (p<.0082)	80.6%
Blood fusion required	2.5%	6.8%
Dose adjustments per week	2.7	3.6
Adverse events		
Hypertension	14%	13%
Nasopharyngitis	10%	10%
Diarrhea	7%	13%
Peripheral edema	7%	13%
Drug-related antibodies	0	0
Post hoc analysis		
Patients with at least 1 Hgb value >13 ***in the first 8 weeks***	12.4% (p<.0001)	33.5%

Comments about CERA and this trial included:

- *Florida:* "I'm very open to Mircera."
- *Canada (CERA investigator):* "Our study nurse noticed there were fewer patients overshooting the Hgb target – which officially is 11-13 but for me is 11-12 – CERA is slower to raise Hgb, but what's the rush?...I'm excited about a once-monthly injection, which fits well with home dialysis. CERA is not as much a no-brainer in dialysis centers as in home dialysis."
- *Michigan (CERA investigator):* "Under the current reimbursement schedule for ESAs, the more injections you give, the more you make. Unless that method changes, there is no advantage (in dialysis patients) of one product over the other. But CMS is looking at bundling methodology, and if that comes about, frequency of administration will have a major impact on the choice of agent…In CKD, everyone will switch to CERA. In dialysis, it will be up to the (dialysis) chains."
- *U.K. (Dr. Iain Macdougall, a CERA investigator):* "There is a huge advantage for CERA on Hgb. It has superiority (over Aranesp) on Hgb overshoot, but there are a lot more advantages to CERA than that. In CKD, the advantages are for the patient – stability, less frequent dosing, and fewer dose adjustments…In the dialysis population, the advantages are less nursing time, which translates into a huge cost advantage. Otherwise, there is no advantage (in dialysis patients)…There are no data yet, but anecdotally, there is no stinging with CERA, and there is stinging with Aranesp."
- *North Carolina:* "I like the idea of competition (in ESAs) – to drive down prices. I'd also like to see Fibrogen and hematide succeed. We could eventually have patients do their own hemoglobin test at home and call it in or email in the results. There is a test that could do this now."
- *California:* "I need more information before I make up my mind about this. I'm still concerned about safety. CKD or PD (peritoneal dialysis) would be more receptive than dialysis."

Asked whether CERA is likely to help maintain patients in a tight Hgb range (11-12), an investigator said, "We found the actual time in target is longer with a longer acting agent – CERA…Overshoots can be minimized by a longer-acting agent."

Asked about the exclusion of high CRP patients from this trial, an investigator said, "Only 3% of CKD patients have high CRP." Another investigator said, "The CRP exclusions should not be criticized."

2. AMICUS – Q2W IV CERA dosing in CKD patients on dialysis vs. Epogen. The efficacy of CERA (starting dose 0.40 µg/kg IV every two weeks) was compared to Amgen's Epogen (3x/week IV) in 181 ESA-naïve dialysis patients for 24 weeks. Researchers concluded CERA is effective at correcting anemia, provides a smooth and steady Hgb increase, and is safe and well tolerated.

CERA vs. Epogen in Dialysis Patients

Measurement	CERA IV Q2W n=135	Epogen IV TIW n=46
Baseline Hgb	9.39 g/dL	9.40 g/dL
Primary endpoint #1: Hgb increase of ≥1 g ***and*** a single measurement Hgb ≥11 by ITT	93.3%	91.3%
Primary endpoint #2: Mean change in Hgb from baseline	12.1	12.0
Mean dose at time of response	0.60 µg/kg/2wk	123 IU/kg/2wk
Patients with Hgb >13 at any time	59.2% (p=Nss)	60.9%
Blood fusion required	5.2%	4.3%
Adverse events		
Hypertension	19%	24%
Procedural hypotension	7%	7%
Arteriovenous fistula thrombosis	5%	9%
Drug-related antibodies	0	0
Post hoc analysis		
Patients with at least 1 Hgb value >13 ***in the first 8 weeks***	8.2% (p=0.0953)	17.4%

3. MAXIMA – QM IV CERA dosing in dialysis patients vs. Epogen. Two posters were presented on this open-label, randomized, multicenter, parallel group, 1-year, Phase III trial comparing IV CERA either once every two weeks or once monthly to Epogen administered 1-3 times a week. The trial also examined crossover from Epogen to CERA. The conclusions were that once-monthly CERA is as effective as Epogen in maintaining stable Hgb levels, regardless of gender, age, or diabetic status, and patients who crossed over from Epogen to CERA also maintained stable Hgb levels.

4. Binding affinity of CERA vs. Epogen. *In vitro* studies were presented that indicated CERA acts differently at the receptor level than Epogen, with lower EPO binding affinity and higher EC_{50} for cell stimulation.

5. PROTOS – QM SC CERA in dialysis patients converted from Epogen SC. This was an open-label, randomized, multicenter, parallel-group Phase III study in 572 patients. In one poster, the conclusion was that patients can be successfully transitioned from SC Epogen administered 1-3 times a week to once-monthly SC CERA, and CERA SC once-monthly maintains stable Hgb levels on both a group and an individual basis. In another poster, CERA, like Epogen, effectively maintained stable Hgb levels regardless of age, gender, or diabetic status. Researchers concluded that CERA can be used to treat patients with a wide range of characteristics.

INTRAVENOUS IRON

ADVANCED MAGNETICS' ferumoxytol

The Phase III data looked very good for this semi-synthetic, ultrasmall superparamagnetic iron oxide coated with poly-glucose sorbitol carboxymethylether. Each vial of the drug contains 30 mg/mL of iron and 44 mg/mL of mannitol, with no preservatives. Ferumoxytol appears equally or more efficacious than current products but easier to administer.

An open-label, randomized, multicenter Phase III trial compared 510 mg ferumoxytol to 200 mg oral iron daily for three weeks in a total of 304 patients at 20 U.S. sites. Ferumoxytol was administered in two 17-second IV injections over 5 days. Company officials said the full data will be published next year in a major journal. The poster with this data was labeled a pooled analysis of two Phase III trials, but a company official said that was a typographical error, and the company was only reporting on data from one trial.

Researchers concluded:

- The safety profile was comparable to oral iron, with no drug-related serious adverse events.

Pooled Ferumoxytol Phase III Results

Measurement	Ferumoxytol 510 mg n=228	Oral iron 200 mg n=76
Evaluable for safety	96.2% *	98.7% *
Evaluable for efficacy	79.8%	73.7%
Stage 1 (eGFR ≥90)	0.4%	1.3%
Stage 2 (eGFR 60-89)	1.3%	1.3%
Stage 3 (eGFR 30-59)	36.0%	39.5%
Stage 4 (eGFR 15-29)	46.9%	47.4%
Stage 5 (eGFR <15)	13.6%	10.5%
Baseline ferritin	146.1	143.5
Baseline hemoglobin	9.96 g/dL	9.96 g/dL
Results		
Primary endpoint: Hgb mean change from baseline at Day 35 by ITT	0.81 (p=0.002)	0.21
Hgb mean change from baseline at Day 35 in evaluable patients	0.86 (p<.0001)	0.06
Secondary endpoint #1: Patients achieving ≤1 g/dL decrease in Hgb at Day 35 by ITT	36.6% (p=0.0026)	19.7%
Evaluable patients achieving ≤1 g/dL decrease in Hgb at Day 35	42.3% (p=0.0004)	16.1%
Secondary endpoint #2: Mean change from baseline in serum ferritin at Day 21 by ITT	514.9 (p<.0001)	6.5
Mean change from baseline in serum ferritin at Day 21 in evaluable patients	551.0 (p<.0001)	8.9
Safety		
Adverse events	35.5%	52.0%
Drug-related adverse events	10.6%	24.0%
Serious adverse events	4.6%	9.3%
Drug-related serious adverse events	0	0

* Patients excluded from analysis did not receive study drug

- Ferumoxytol delivers a higher amount of iron per dose than any other current IV iron therapy and is well tolerated.
- Patients getting ferumoxytol showed a significantly greater increase in Hgb at Day 35 and in serum ferritin at Day 21.
- A significantly greater percent of patients achieved a ≥1 g/dL increase in Hgb at Day 35.

However, several issues deserve attention:

➢ **Lack of physician excitement.** Investigators, not surprisingly, were very enthusiastic about this drug. One said, "I really think efficacy is better with ferumoxytol." Another said, "I would use this exclusively if it were approved. It is a lot easier dosing regimen."

However, most nephrologists (non-investigators) who were questioned about its outlook were somewhat cool to it. They insisted that the less frequent dosing with ferumoxytol isn't a significant advantage.

- *U.K.:* "I'm very happy with Venofer (American Reagent, IV iron sucrose). There isn't that much need for a new iron. Cost would decide my use."
- *Georgia #1:* "I would look at it, but it can't be another me-too. Fewer doses would be an advantage for outpatients (CKD), but I'm not sure of the need in dialysis patients. In dialysis it would have to show a better ESA response or less intolerance of an ESA."
- *California:* "I don't see what's better about this. Two injections instead of 4-5 may not have appeal."
- *Georgia #2:* "It isn't an important product. You can give other irons slower. And it will be a cost issue."
- *Ohio:* "I don't see any need for it, and cost will be an issue…Also most nephrologists don't infuse drugs in their office."
- *New Jersey:* "I'm interested, but I probably wouldn't pay more for it (than the Venofer I currently use)."
- *Texas:* "I think it is a good product. Having a product easier to administer would increase (IV iron) use."
- *Pharmacist:* "In general, there is interest in giving iron faster, but only if it is safe. This has potential if it is safe."

A competitor said, "You don't need high dose iron in hemodialysis patients, and there are no studies to show CKD and PD patients need 1 g iron and then only once every 6-12 months…Ferlicit (Watson, IV sodium ferric gluconate) is given in 250 mg doses, and not all patients need four doses (1 g). Some patients only need 1 or 2 injections of Ferlicit in CKD…Cost also may be an issue. Insurance companies may say ferumoxytol is too expensive."

➢ **Adverse events.** Safety is the regulatory hurdle for this drug, and the company declined to characterize what type of adverse events were seen. Two officials insisted they didn't know the nature of the adverse events because the reporting was handled by a contract research organization (CRO), but CEO Dr. Brian Pereira said the company does have that data but would not discuss it because of SEC rules (Regulation FD on full disclosure). Dr. Pereira said more details on the adverse events were not included on the poster because there wasn't room, though some companies have solved that problem with an asterisk and a statement such as "mostly mild-to-moderate nausea," etc. However, Dr. Pereira did say there were no cardiac adverse events with ferumoxytol in this trial.

Three years ago, Advanced Magnetics presented data at ASN from a single-site, single-dose, open-label Phase I study of ferumoxytol in 10 dialysis patients. In that safety study the drug-related adverse events were vomiting and hypotension, and there were no allergic reactions.

➢ **Serious adverse events.** The company insisted there have been no serious adverse events, but a source said there was one case of anaphylactoid reaction. According to that source, the company did not agree with the investigator's classification of the event as an anaphylactoid reaction, and, thus, did not report it, and the investigator then reportedly pulled out of the trial and took all of his patients out of the trial.

How big a concern are anaphylactoid reactions to the FDA? Speaking in general terms, an FDA official said, "The interpretation of important but uncommon hypersensitivity or infusion reactions is challenging…Hence, it is probably impossible to focus entirely upon any one aspect of the risk consideration exclusive of the other considerations. In general, modest treatment benefits should correlate with minimal risk for toxicity." The FDA will consider:

- The nature of the responses. Fatal reactions are far more important than less serious reactions.
- The management. Some reactions are readily handled by co-treatments or preventive treatments.
- The frequency of the events and the nature of the drug's treatment benefit, for example, life-saving vs. symptomatic treatment.

➢ **Competition.** The poster claimed that ferric gluconate is no better than oral iron at improving Hgb in CKD patients, but Watson officials disputed that. The poster also characterized the data on Venofer as "conflicting," but nephrologists disputed that, too, insisting Venofer has been shown to be effective.

Three other Phase III ferumoxytol trials are underway, and the results of those will be reported in the future. They are:

1. **Safety in dialysis and pre-dialysis.** This crossover trial comparing ferumoxytol to placebo is closed.
2. **Pre-dialysis.** The last patient has been enrolled, but that patient still needs a 35-day check to say this trial is closed.
3. **Dialysis.** This trial is ongoing, and a company official said it will be the longest to complete, "It is more difficult to enroll patients in this trial because entry criteria include Hgb <12 and on dialysis for several months.

PHOSPHATE BINDERS AND TREATMENT OF HYPERCALCEMIA

Nephrologists have three options to lower phosphorus in dialysis patients: Genzyme's Renagel (sevelamer), Shire's Fosrenol (lanthanum carbonate), or a calcium-containing phosphate binder like Fresenius's PhosLo (calcium acetate), which Fresenius bought from NABI Biopharmaceuticals on November 14, 2006, just two days before ASN. For hypercalcemia, Amgen's Sensipar (cinacalcet) is a relatively new option.

Nephrologists questioned at the ASN meeting said:

- Use of **Renagel** is increasing.
- Use of **Fosrenol** is relatively flat.
- Fresenius's purchase of **PhosLo** is not expected to affect use of PhosLo either positively or negatively.
- **Sensipar** use is limited by cost, but Medicare Part D coverage is helping use somewhat.

Among the comments were:

- *Georgia #1:* "A lot of patients don't get Sensipar (for the treatment of hypercalcemia) because it is too expensive. Sensipar 90 mg/day costs $849.86/month, and 60 mg/day costs about $600/month. In comparison, 50 tabs of Renagel costs about $80/month, and 9 Renagel tabs a day costs about $440/month…Renagel use is going up because studies are showing it might lower calcium deposits in the heart…Fosrenol is a last resort; I'm still not sure it is safe…The amount absorbed is more than the company told the FDA…I asked Fresenius about PhosLo, and they insisted there would be no difference in access for patients. Fresenius just says its strategy is to diversify, and this is their entry to more pharmaceuticals. I don't think Fresenius owning PhosLo will affect use."
- *Georgia #2:* "Cinacalcet use is increasing. I find more and more plans are covering it. We treat prisoners, and until this year, they were the only (dialysis patients) who could get it…Renagel and Fosrenol are in a hand-to-hand fight. I use both. I'm a big fan of non-calcium binders. But I have patients who hate chewing Fosrenol, and patients who hate the number of pills with Renagel…My calcium binder use is going down. I think Fresenius bought PhosLo thinking they could force us to use it, but they said they won't do that, so I don't know why they bought PhosLo."

- *New Jersey:* "I use a lot of Renagel and PhosLo, but little Fosrenol because of the GI side effects, though I use it in patients with a poor response to Renagel or PhosLo."
- *U.K.:* "I never use Sensipar because of the expense. I don't use Fosrenol either."
- *Florida:* "I'm using more cinacalcet since Medicare Part D started because patients can't afford it without insurance…My Renagel use is also steadily going up."

INEOS HEALTHCARE'S Alpharen

A Phase IIb trial in dialysis patients is expected to finish in 1Q07 of this investigational phosphate binder. The potential advantages were described as: more efficacy at lower doses than Renagel and a lower pill burden (1-2 per meal).

KERYX BIOPHARMACEUTICALS

➢ Zerenex (ferric citrate)

Nephrologists generally were unaware of this new phosphate binder in development, but the doctors questioned about it were open to a new phosphate binder that doesn't use lanthanum, aluminum, or calcium. Zerenex was in-licensed from Panion & BF Biotech in Taiwan. In animals, the binding capacity of ferric citrate is 80-90 mg per gram of elemental iron, which was described as comparable to other phosphate binding agents currently on the market.

A Keryx official presented data from a randomized, double-blind, placebo-controlled, dose-ranging Phase II study in ESRD patients, and it looked promising. In the 116-patient trial, conducted in Taiwan and the U.S., all patients underwent a two-week washout of all phosphate-binding agents. The drug was administered with meals TID for 28 days. All patients on ferric citrate experienced a change in their stool color. Asked why there were so few GI side effects in this trial, the Keryx official pointed out that ferric citrate is a trivalent iron, "What we believe is happening is the iron is taken with food, and when it dissociates with citrate, it is almost immediately taken up by phosphate. That is different from ferrous (iron) which is taken on an empty stomach, so (with ferric citrate), you avoid the GI side effects. That is our hypothesis at this point."

The KDOQI guidelines recommend serum phosphorus in dialysis patients be maintained in the 3.5-5.5 mg/dL range.

A Phase III trial is planned, and the company hopes to gain approval based on a single Phase III trial – along with the Phase II safety data and substantial enrollment in a Phase IV macroalbuminuria trial (ongoing). The 6 mg/day dose will be used in this trial, with safety data collected out to one year.

No change in the acid base status of patients was observed in the Phase II trial, but that will be monitored in the Phase III trial. Asked what size pills or pill burden will be used in the Phase III trial, the Keryx official said, "We plan to use capsules in Phase III, but we also will use other alternative formulations, which we won't disclose. One of the issues we are aware of is compliance with the size of the capsule. So it is in our own best interest not only to have capsules but to have other user-friendly formulations to improve compliance."

➢ Sulodexide

A Phase III trial of sulodexide – which is being done under a Special Protocol Assessment (SPA) with the FDA – uses microalbuminuria as an endpoint, and sources generally thought that was an acceptable endpoint. Officials would not say what p-value that trial would have to have to allow approval on only one Phase III trial, though one source conceded it has to be lower than p<.05. This source also indicated that the trial is 95% powered to show a 25% effect with drug vs. a 15% effect with placebo.

♦

Phase II Ferric Citrate 28-Day Results

Measurement	Placebo n=16	2 g/day FC TID n=33	4 g/day FC TID n=34	6 g/day FC TID n=33
Available for ITT analysis	16 patients	31 patients	32 patients	32 patients
Serum phosphorus on Day 0	7.2	7.2	7.1	7.3
Serum phosphorus on Day 28	7.1	6.9	6.0	5.9
Change in serum phosphorus vs. baseline	-0.1	-0.3	-1.1	-1.5
Any adverse event	43.8%	48.5%	35.3%	51.5%
Drug-related adverse events	25.0%	24.2%	29.2%	30.3%
Serious adverse events	6.3%	0	5.9%	N/A
Diarrhea	12.5%	9.1%	2.9%	3.0%
Abdominal pain	0	0	11.8%	6.1%
Stool discoloration	6.3%	2.9%	9.1%	4.3%
Vomiting	0	6.1%	2.9%	3.0%
Constipation	0	0	5.9%	3.0%