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By Lynne Peterson

SUMMARY

Shire has completed more than 80 studies attesting to the safety of Fosrenol (lanthanum), but a competitor, Genzyme, found liver and kidney accumulation in rats and is sending that data to the FDA, which could delay Fosrenol approval. When Fosrenol is approved, it is likely to significantly impact sales of Genzyme's Renagel because it has a lower pill burden and the pills are chewable. ♦ The concern about PRCA with Johnson & Johnson's Eprex has abated now that it is given only IV. The Phase II data on Roche's pegylated erythropoietin, CERA, looked very good. ♦ Amgen/NPS's calcimimetic, cinacalcet, is likely to be a big hit – provided it isn't priced out of the market. Cinacalcet is likely to decrease use of vitamin D analogs but not phosphate binders. ♦ Cost will be a huge factor in the outlook for any new agent in nephrology.

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AMERICAN SOCIETY OF NEPHROLOGY

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This articles focuses on four selected topics discussed at the American Society of Nephrology meeting:

1. **Hyperphosphatemia**, particularly Shire's Fosrenol (lanthanum)
2. **Anemia**, with emphasis on Hoffmann-La Roche's CERA
3. **Hyperparathyroidism**, with a look at Amgen's cinacalcet (AMG-073) and Abbott's oral Zemplar (paricalcitol)
4. **CMS reimbursement** changes for ESRD

HYPERPHOSPHATEMIA

SHIRE'S FOSRENOL (lanthanum carbonate)

Lanthanum is a rare earth element (a heavy metal) that is detectable in most humans due to chronic low exposure. Shire, which licensed Fosrenol from AnorMED, submitted it to the FDA in April 2002 to treat hyperphosphatemia. Elevated phosphate levels in the blood often occur in end-stage renal disease (ESRD) patients on dialysis. Estimates are that more than 250,000 Americans are on dialysis patients, and as many as 80% of these develop hyperphosphatemia. If untreated, hyperphosphatemia can lead to renal osteodystrophy, which causes bone pain, skeletal deformities, and even fractures. Hyperphosphatemia also has been associated with the development of cardiovascular disease. In addition to diet, patients typically take either calcium carbonate or Genzyme's Renagel (sevelamer hydrochloride).

In March 2003, the FDA issued an approvable letter for Fosrenol but asked Shire for additional long-term safety data. Shire presented numerous posters at the ASN meeting demonstrating the safety of lanthanum, and an official said the company has been has been collecting this data since the filing and will be submitting the data to the FDA before the end of 2003. Another official said the company has done more than 80 toxicology studies and has not found any lanthanum accumulation in the brain and no measurable amount in CSF, though there is some small accumulation in bone and liver, "Lanthanum can't cross the blood brain barrier intact." A Shire official said all the toxicology data on lanthanum has been sent to a major journal for publication.

In addition, Shire sponsored an evening symposium at which a speaker made several points about lanthanum, including:

- Only 0.00089% of lanthanum is absorbed in humans.

- What happens when these small amounts are absorbed? It is extensively bound to plasma proteins (99.7% bound). In distribution studies of more than 40 tissues in mice, rats and dogs for up to 80 weeks, the majority had concentrations of <1 µg/g, with the highest concentrations in the liver and bone, though those were still <10 µg/g.

- It is >99% excreted in feces, with minimal urinary excretion (0.000031%). The absorbed fraction is excreted mostly in bile (80%).

- The area under the curve is not different for dialysis patients compared to normal individuals.

- The pill burden will be low. With 1 g dose and a maximum dose of 3 g, patients will only have to take three pills a day – and they are chewable.

- With one-year therapy, a significant number of patients achieve the desired phosphate control, with less hypercalcemia.

- There are no aluminum-like effects.

- Total exposure to lanthanum is known in 1,754 patients:
  - 6 months in 996 patients.
  - >12 months in 604 patients.
  - >18 months in 299 patients.
  - >24 months in 205 patients.
  - >36 months in 33 patients.

- Eleven Phase I, 10 Phase II and III, and two long term safety studies are ongoing. A large, ongoing, two-year safety/efficacy study of lanthanum has a subgroup that got biopsies, and preliminary one-year data found lanthanum did not have either an adverse or a positive effect on bone: 33% improved, 36.7% were unchanged, and 30.6% worsened.

Most Common Lanthanum Adverse Events

Adverse Event	Lanthanum n=533	Calcium n=267
Hypercalcemia	0.4%	20.2%
Hypotension	7.5%	9.0%
Headache	5.1%	6.4%
Constipation	6.0%	6.7%

Experts answered audience questions about lanthanum, including:

How do organs get rid of lanthanum, so it is not the same problem as aluminum?
"A very small amount is being absorbed…and 80% of that is excreted in the bile…plus a minute amount in the urine…The fear is that this might be another aluminum…but that is pretty much dispelled by the lack of accumulation, except in bone and liver and then only on the order of 1 ppm…And there is no liver toxicity out to three years…There was data in Europe where a bone lab looked at it in a blinded fashion and couldn't find any aluminum-like effects either…So, it appears bone is a storage place for trace elements, without any toxic effects."

One-Year Results of Lanthanum Bone Biopsy Study

Adverse Event	Lanthanum n=100	Conventional therapy n=97
Mean age	50.2	55.3
Hypercalcemia	60%	82%
Nausea	25.0%	28.9%
Vitamin D usage	Not reduced	N/A
Secondary endpoint #1: Control of Ca x P	---	Significantly higher throughout the study
Secondary endpoint #2: PTH	Higher	---
Bone alkaline phosphate	Higher	---
Improvement or no change in bone abnormalities	70%	44%

Will lanthanum reverse calcification in humans?
"Probably not."

Is there a relationship between bone turnover and extra-osseous calcification?
"We don't know, but it is vascular calcification that probably contributes to the cardiovascular mortality in renal patients…Vascular calcification occurs at two major sites – the media and the intima…and it can be diffuse, or there can be real bone formation in the vessel wall…The evidence indicates vascular calcification is a regulated process, similar to the way bone calcification is regulated."

Is there a connection between bone metabolism and vascular calcification?
"Framingham showed patients with osteoporosis also developed vascular calcification…(There is) a controversial idea that the mechanism is a systemic process."

A Competitor's Perspective

However, Genzyme painted a very different picture of the long-term safety of lanthanum finding that it does accumulate in the body. Genzyme researchers did their own animal study, putting lanthanum (3%) in the dry food of 11 renally compromised rats for 28 days. They then sacrificed the rats and analyzed their tissues by microwave degradation. A researcher said, "We see significant deposition of lanthanum in the liver and kidney. Shire studies used a less severe model of renal failure. Our model is more renally compromised, and we put the lanthanum in the animal feed, which certainly is more of a real world study for ESRD…It is hard to know the functional implications...Lanthanum deposition is higher in normal rats as well as renally compromised rats, but it is significantly more than normal rats…We found a statistically significant amount of lanthanum in the lungs and bone but not in blood, brain, heart or spleen of renally compromised rats."

Shire officials and researchers disputed the Genzyme findings. Two criticisms were: (a) The way the lanthanum deposition was measured, and (b) contamination. A source said, "Lanthanum from the feed could have gotten onto the fur of the rats and contaminated them."

Genzyme researchers found:

- Lanthanum accumulated in the kidney, liver and lung tissue of these rats, despite non-detectable changes in blood levels.
- Lanthanum deposition is enhanced in uremic vs. non-uremic rats.
- The most deposition occurred in the liver, with levels approached 10% of normal calcium levels.
- Blood levels are a bad measure of lanthanum accumulation.

Tissue Deposition of Lanthanum

Tissue	Control n=4 (ppm wet weight)	Lanthanum Treated n=7 (ppm wet weight)	Fold increase
Scapula	0.1022	0.0853	---
Femur	0.037	0.0581	---
Kidney	0.0021	0.0082	4
Spleen	0.0032	0.0214	7
Heart	0.0016	0.0122	8
Lung	0.0013	0.0275	20
Liver	0.0015	0.0950	60
Brain	0.0015	0.2449	167

Genzyme sent its data to the FDA, which may muddy the regulatory water for Shire and possibly delay final approval of Fosrenol. A Genzyme official said the company believes that lanthanum does accumulate in the brain, and they are doing additional studies to try to prove that. Genzyme plans another trial, this time in 5/6 nephrectomized rats (rats with all of one kidney and one-third of the other removed). There appears to be a precedent for a company studying a competitor's drug prior to approval -- Pfizer reportedly sent the FDA some toxicity data on Lilly's Cialis (tadalafil) – but it is a highly unusual step. FDA officials were questioned about how they would view safety data coming form a competitor, and they all agreed, "We are always interested in new data, regardless of where it comes from." *(NOTE: These sources include the FDA's Dr. Bob Temple.)*

Physician Reaction

Physicians are interested in lanthanum, but many will approach it cautiously until safety issues are clearer. The key points doctors made were:

- Fosrenol appears to have better efficacy than Renagel.
- The lower pill burden is a huge advantage for Fosrenol.
- Cost will be very important.
- Safety is a concern. Doctors want to be sure this will not be a repeat of what happened with aluminum. At the same time, though, sources were not overly worried about the safety of lanthanum. Most sources said they will approach usage cautiously if it is approved, but FDA approval would give them a fair level of reassurance of the safety.
- Initially, it is most likely to be used for new patients; doctors do not plan to switch patients doing well on Nabi Biopharmaceuticals' PhosLo or Genzyme's Renagel.
- Renagel is the only drug likely to be negatively impacted by Fosrenol.

GENZYME'S RENAGEL (sevelamer hydrochloride)

Nephrologists said that:

- The new KDOQI guidelines would have little impact on Renagel use?
- They were unimpressed with the cardiovascular data so far. If it is proven that Renagel has a mortality benefit, then they would use it first lien in patients with drug coverage.

Miscellaneous

Other phosphate binders in development to compete with Renagel include:

- **Mitsubishi Pharma's MCI-196.** This is in Phase II trials in the U.S. Its action reportedly is weaker than Renagel, but the side effects also are supposed to be less – and a researcher said it would be "much cheaper."
- **ML Laboratories'** novel phosphate binder. This inorganic, layered, crystalline salt would also be cheaper than Renagel because it is less expensive to manufacturer, according to a researcher. Phase I trials are complete, and the product is moving into a Phase IIa trial. The dosage form has not yet been finalized, and a researcher said, "It is too early to see if this can lower the pill burden."
- **Nabi Biopharmaceuticals' PhosLo**. The one-year PRECISE trial in patients who have been on dialysis <3 years is due to start In 1Q04, comparing Lipitor+PhosLo to Renagel. Patients will be taken off all Vitamin D analogs and vitamin supplements. *(NOTE: Nabi has a staphylococcus vaccine for dialysis patients and officials said they thought phosphates would be a good "in" to ESRD.)*

  Nabi officials said PhosLo has some advantages over Renagel, including:

  - PhosLo doesn't cause "acid loading," and Renagel does. An official said, "This can have negative effects on bone and on protein metabolism."
  - The new KDOQI guidelines want the bicarbonate in the blood >22, and 85% of Renagel patients are <22.

ANEMIA

Changes in epoetin usage were not discussed at the session with CMS officials (see CMS section of this report), but a source said that CMS is running some pilot programs to change the capitated epoetin rate. Reportedly, these programs will offer incentives to dialysis clinics to reduce the epoetin dose. The agency also is "totally re-evaluating our epo policy" at the current time, and this is supposed to be completed January 15, 2004. Asked why CMS is reviewing the epoetin payment policy now, an official said, "Any major policy should be reviewed periodically. It should happen every few years."

A poster reporting on one-year epoetin mortality rates found that lower hematocrits and higher epoetin doses were associated with decreased survival. A doctor who viewed this poster commented, "I'm not going to push the epo dose as much after seeing this."

PRCA

The pure red blood cell aplasia (PRCA) that has been associated with subcutaneous administration of Johnson & Johnson's Eprex (recombinant human epoetin alpha) was a topic of keen interest at the meeting, but most doctors were not overly worried about it. Most European doctors questioned about their use of Eprex said they have already made the switch to subcutaneous Eprex, and they did not expect usage to further decline. U.S. doctors generally were aware of the issue, but many were following it only peripherally since Eprex is not sold in the U.S.

The doctor who first reported the Eprex PRCA offered an update on the situation to a packed room. Among the points she made were:

- Since 1998, there have been 198 cases of PRCA reported world-wide:
  - 169 in Eprex patients alone
  - 6 cases with Procrit alone in the U.S.
  - 8 cases with NeoRecormon only
  - 15 cases in patients with both Eprex and another epo
  - 0 cases with Aranesp
  - Median time from first exposure to PRCA is nine months (range 3-90 months)
  - No patients have gotten PRCA who had only been exposed to IV Eprex
- The incidence of antibodies is low, but all antibodies tested were found to be neutralizing, even when the level was very low. There were various binding capacities, but even the lowest binding capacity is very high. PRCA is clearly linked with the presence of anti-EPO antibodies. Cryopreserved sera from eight patients obtained before development of PRCA were found to be negative for antibodies.
- In patients who got PRCA, switching from subcutaneous Eprex to IV Eprex or to NeoRecormon did not resolve the problem.
- Virtually all the cases were observed in renal patients, though there were two cases in MDS patients that were not discussed at the ASN meeting.
- The incidence of PRCA sharply decreased since European doctors changed from subcutaneous to IV administration of Eprex in December 2002. In 2003, only five cases have been reported, and not all were induced by Eprex.
- The PRCA issue should have considerable implications for the future approval of epoetin preparations and other biopharmaceuticals.
- In Japan, the clinical picture of patients and the behavior of the antibody is the same, but there have been some patients without a clear bone marrow picture of PRCA, though they have neutralizing antibodies.

A researcher with the PRCA Study Group discussed efforts to treat antibody-mediated (epo-induced) PRCA patients. The group studied 45 epo-related cases of PRCA in CKD patients. They concluded there is no recovery without immuno-suppressive therapy (cyclosporine or corticosteroids+/-cyclophosphamide):

- There was no relationship to underlying nephropathy.
- It is not a disease of resistance to epoetin.
- Of nine PRCA patients who went untreated, none recovered.
- Of the 36 treated patients, 80.5% recovered:
  - 11/15 who got corticosteroids alone
  - 0/4 who got a corticosteroid+IVIG
  - 7/8 who got a corticosteroid+cyclophosphamide
  - 1/9 who got only IVIG
  - 1/1 who got plasma phoresis (but the speaker said he is not proposing this therapy, "We have no data to support this."
  - Five patients got a kidney transplant, and all of these recovered soon after transplantation, but they all got cyclosporine or FK-506.

A U.K. doctor in the audience said a number of U.K. patients have recovered from epo-induced PRCA without treatment. However, the presenter said he did not see any recovery in the U.K. patients in the study group cohort, but all the U.K. PRCA patients were not included in the cohort. He said, "It is hard treatment, but in our study no patient recovered without it."

ROCHE'S Continuous Erythropoiesis Receptor Activator (CERA)

Roche already has the largest share of the European market for erythrypoietin with its NeoRecormon (epoetin beta), and

company officials have indicated Roche plans to enter the U.S. market with a new epoetin, CERA. CERA is a single chain polymer and a huge molecule, just over 60,000 Daltons vs. EPO at just over 30,000 Daltons, making it roughly twice the molecular size of EPO.

Researchers presented Phase II data from a 12-week, open-label study of subcutaneous CERA, a pegylated erythropoietin, in dialysis patients with chronic anemia, and the data looked very good**.** Patients were divided into three groups, with three dosing intervals in each group. After 6 weeks individual dose adjustments were permitted. The data indicated CERA delivered potent and sustained stimulation of red blood cell formation at dosing intervals as long as once every three weeks. CERA demonstrated a good safety profile in all treatment groups, and it increased hemoglobin at all doses studied, with a clear dose response curve.

12-Week Phase II CERA Results

Hemoglobin	CERA 0.15 g/kg QW 0.30 g/kg EOW 0.45 g/kg E3W	CERA 0.30 g/kg QW 0.60 g/kg EOW 0.90 g/kg E3W	CERA 0.45 g/kg QW 0.90 g/kg EOW 1.35 g/kg E3W
Hb rise of ≥1 g/dl	>70%	>90%	>90%

On reticulocytes:

- With epo, a single 20 µg/kg dose causes a brisk effect that peaks at Day 4 and is over by Day 6, and with repeated epo dosing, there are repeated peaks.
- With a single CERA dose, the reticulocytes followed initially the same kinetics, but by Day 4 there were more reticulocytes and the duration of response lasted 11 days.
- Thus, the magnitude and duration of response was greater with CERA than with an equivalent amount of epo beta.

On red blood cells:

- With epo, a single dose caused essentially no change in RBCs. It takes repeated administration four times a week to see a significant increase in RBCs.
- With CERA, a single administration of 20 µg/kg, causes a rise in RBCs that is sustained out to 16 days before it begins to decrease.

CERA has been tested in more than 300 patients in Phase I trials, about 350 patients in Phase II trials, and a Phase III trial of 1,700 patients (1,200 to be treated with CERA) was due to start before the end of 2003. CERA appears to act in a somewhat different manner from other epos. A researcher explained, "Epo disappears by being internalized after it binds to the receptor…The hypothesis is that epo acts on the receptor to stimulate erythropoiesis…There is some data that CERA acts in a slightly different way…It does bind to the receptor and stimulates erythropoiesis, but it comes off the receptor and perhaps can attach to other receptors and cause more continuous stimulation of erythropoiesis…CERA is not internalized, and we think epo may be…We think CERA can't get in because it is too big…and then the polymer is metabolized by the liver."

Asked about concern with PRCA, a researcher said, "A critical concern of FDA will be sensitive assays of antibody production, but I think the happy news here is that in Phase I and Phase II there hasn't been a single patient with antibody production demonstrated."

Other points speakers made:

- No antibodies have been seen yet with CERA, but a researcher said this may be simply that it hasn't been studied long enough.
- It appears the IV and subcutaneous dynamics of CERA are very similar.
- In a rat study, CERA 2.5 µg/kg weekly was similar to epo 2.5 µg/kg three times a week, and CERA 2.5 µg/kg weekly has a similar effect on RBCs to epo 2.5 µg/kg three times a week.
- CERA has a lower systemic clearance than epo, resulting in a longer elimination half-life.

Half-Life of Various Epoetins

Mean Half Life	IV	SC
Epo alpha	6.8 hours	19.4 hours
Epo beta	8.8 hours	24.2 hours
Aranesp	25.3 hours	48.5 hours
CERA	133 hours	137 hours

CERA in 5/6 Nephrectomized Rats

Measurement	CERA Rats n=3 Dogs n=4	Epo Beta Rats n=9 Dogs n=10
Clearance in rats	1.5 hours	14 hours
Clearance in beagles	0.8 hours	8.6 hours
Half life in beagles	41 hours	6.4 hours

A researcher from Spain reported that subcutaneous CERA has potent activity. Her reported on Study BA16260 in Stage 5 dialysis patients. Patients were started on low dose, increased to intermediate dose after six weeks, and then upped to high dose after another six weeks. There were no serious adverse events related to study treatment (2 unrelated deaths), and no evidence of antibodies.

Phase I/II clinical study results with CERA in the oncology setting will be presented at the American Society of Hematology meeting in San Diego in December 2003. Phase III studies in renal patients are scheduled to begin in both Europe and the U.S. in early 2004. **Roche also has a synthetic protein in Phase I trials.**

Measurement	CERA Low dose 0.15 g/kg QW	CERA Intermediate dose: 0.15 g/kg every two weeks	CERA High dose 0.15 g/kg every three weeks
Mean Hb increase	.78	1.36	1.24
Hb increase at 6 weeks	1.01	.94	1.43 *
Total adverse events	12	26	22
Vascular disorders	0	0	6
GI	2	5	4
Infections	2	1	3
Nervous system disorders	0	4	2
Musculoskeletal disorders	0	3	1

*** only 2 doses**

The one concern with CERA may be the way reticulocytes drop as CERA wears off. Reticulocytes rise higher and stay high longer with CERA than other erythropoietins, but when they do come down, they seem to crash, going below control, which doesn't happen with a similar product. This may only mean that patients will have to be careful not to miss doses with CERA. That probably means, taking CERA on time, with less margin of error.

JOHNSON & JOHNSON'S Procrit/Eprex (erythropoietin alpha)

Two posters discussed how to dose patients who are switched from subcutaneous (SC) to weekly intravenous (IV) Eprex. A study of 111 dialysis patients found that a higher IV dose is not necessary initially, but a slight increase in dose generally is required over the first several months. Another study from Australia found that the Eprex dose needed to be increased 8.8% when going form SC to IV. A Canadian study found that switching from SC to IV Eprex required boosting the dose of Eprex, from 130.02 kg/week initially to 139.69 kg/week at 180 days.

ADVANCED MAGNETICS' Ferumoxytol

Ferumoxytol, iron replacement therapy, was originally developed as an MR imaging contrast agent. It is a superparamagnetic iron oxide coated with a semi-synthetic carbohydrate. A speaker suggested that giving a large, bolus dose of iron allows: (a) quicker reversal of absolute or functional iron deficiency anemia, (b) better compliance, particularly for pre-dialysis patients, and (c) is likely to be more cost effective than other competing therapies.

The results were presented from a single-site, open-label, single dose, Phase I study of 250 mg Ferumoxytol in 10 dialysis patients. The patients did not have to be anemic since this was a safety, not an efficacy, study. The agent was injected over five minutes within 30 minutes of the start of the dialysis session. Researchers reported:

- More remotely-related adverse events (mostly vomiting).
- A statistically significant but clinically insignificant decrease in systolic and diastolic blood pressure.
- Both the doses tested were safe, but future work will focus on the 510 mg dose.
- PK was similar to that in normal subjects.
- No allergic reactions.

HYPERPARATHYROIDISM

Secondary hyperparathyroidism occurs in almost all patients with chronic kidney failure, even before they need dialysis. Thus, in dialysis patients, levels of phosphorus, calcium and vitamin D need to be carefully monitored. The new KDOQI targets, which a speaker described as "challenging indeed," are:

- PTH 150-300
- Serum calcium 9.4-9.5
- Calcium/phosphorus product <55
- Serum phosphorous 3.5-5.5

A speaker predicted that the new guidelines will limit calcium carbonate and calcium acetate use, but increase Renagel use and possibly spur use of Fosrenol. He noted that coronary artery calcification is higher with calcium carbonate and calcium acetate than with Renagel at either 26 or 52 weeks.

Dialysis Patients Achieving KDOQI Targets Over One Month

Measurement	% of patients within range	% in range if criteria liberalized
Calcium	~48%	~73%
Phosphorus	33%	~49%
CA/P product	~57%	~65%
PTH	20%	~43%
All four	~8%	20%

ABBOTT'S Zemplar (paricalcitol)

Most sources view oral Zemplar as a "line extension" for Abbott. They predicted that oral Zemplar would be used primarily for CKD patients prior to the need for dialysis and in CAPD patients. A researcher said that oral Zemplar was likely to be submitted to the FDA in early 2004, but Abbott officials indicated it would be submitted by the end of 2003. A researcher said, "Oral Zemplar will not replace something else. It also causes no hypercalcemia."

Oral Zemplar would be the first oral vitamin D analog with selectivity. Abbott plans to offer it in 2 mcg and 4 mcg capsules. A researcher said that pediatric patients probably will only need one 2 mcg capsule three times a week for long-term maintenance.

For dialysis centers, the choice of Vitamin D analog is mostly a function of contracting – and most sources said they have contracts with Abbott for IV Zemplar. Thus, they did not expect oral Zemplar to have much impact on the dialysis market. Rather, they saw it being used for PD patients and CKD patients. A source said, "Oral Zemplar will have a role in PD, which is about 12% of the dialysis market." A Virginia doctor said, "It is mostly a marketing issue."

Comparison of Vitamin D Analogs

Measurement	Bone Care's Hectoral * (oral and IV)	Abbott's IV Calcijex	Zemplar (oral and IV)
Characteristics	D2	D3	D2
Hypercalcemia	<1%	More	Same
Activation	Delayed. Needs liver (not kidney) pass, so slower peak, which is a"more natural" approach	Active on administration	Active on administration
Cost	Cheaper than Zemplar (30 days ~$70)	Least expensive	Most expensive

*** The company has an approvable letter and is hoping for FDA approval for an indication in Stage II or IV CKD by the end of 2003.**

Results of Phase III Study of Oral Zemplar

Measurement	Zemplar n=73	Placebo n=77
Maximum initial dose	32 mcg (8 capsules 3xWk)	---
Phosphate Binder Dose		
Received Phosphate binder	100%	92% *
Unchanged	85%	86%
Decreased	1%	1%
Increased	11%	6%
Mixed change	3	7
Results of Pediatric Phase III Study		
Number of patients	70	73
Mean initial dose	9 mcg (3 capsules 3xWk)	---
Average maintenance dose by Week 12	6.4 mcg (2 capsules 2xWk)	---
All adverse events	64%	65%
Pain	14%	9%
Abdominal pain	8%	1%

*** 6 placebo patients were not on phosphate binders a baseline or during treatment**

AMGEN/NPS PHARMACEUTICALS' CINACALCET (AMG-073, KRN-1493, NPS-14938)

The FDA has given priority review status to cinacalcet. The cinacalcet data presented at ASN looked strikingly good and was very consistent, and the presentation at the company-sponsored symposium was powerful. Doctors definitely were impressed with this calcimimetic. Most sources said they believe cinacalcet will be approved by the FDA, and they plan to use it – provided their patients have insurance. Cost will be the big limiting factor, they said.

Cinacalcet is ***not*** expected to have much impact on phosphate binders, such as Genzyme's Renagel or Nabi Biopharmaceuticals' PhosLo, but it ***is*** likely to impact sales of vitamin D analogs. When cinacalcet is prescribed, doctors said they do not intend to cut back on use of phosphate binders, but they do plan to reduce the dose of vitamin D. Doctors said new patients with insurance will get cinacalcet, Renagel (or PhosLo), and ***some*** vitamin D (but a lower dose and/or the dose may be titrated down). Vitamin D manufacturers were trying to defend their products, saying there will still be a role for vitamin D analogs, but doctors insisted it will be a much reduced role.

Nephrologists, asked about cinacalcet, said:

- They are very excited about it. When it is approved, they will, at least initially, use it as add-on therapy for patients with iPTH>350. One source said, "I will tend to use cinacalcet early, if not first lien, at least before patients get in trouble with calcium. It will be for both dialysis and secondary hyperparthyroidism patients." A Virginia nephrologist said, "I will use it along with other therapy, probably not first line." A Pennsylvania doctor said, "I'll use it for pre-dialysis patients mostly, or PD patients." A California doctor said, "It will be good for severe secondary hyperparathryoidism patients or PD patients. I don't think carrier will pay for it in primary HPT."
- Vitamin D dosing probably will be lowered when cinacalcet is given, if not initially, then over time. A California doctor was typical, saying, "Cinacalcet will eliminate the need for a vitamin D analog. I'll start patients off on the combination, but then wean them off the vitamin D analog fast."
- Renagel use is not likely to be affected. Sources generally agreed that phosphate binders will still be needed with cinacalcet.
- Cost will be a huge issue. One source said 70% of his patients do not have a prescription drug benefit. One doctor said, Cinacalcet could be first line unless it is too expensive. Then, no one will use it."
- They were very critical of Genzyme for not having a program to help patients who do not have drug coverage for Renagel.

There are 2 types of calcimimetics:

Type 1. This is a true agonist; nothing else is needed to activate it.

Type 2. These are positive allosteric modulators (activators). They depend on the presence of extracellular calcium to work. Cinacalcet falls in this category.

What differentiates cinacalcet from vitamin D are the pulsatile decreases in plasma PTH and the increase in bone mineral density (BMD) with cinacalcet. A speaker said, "In animals, if you infuse the calcium, you don't see much difference from control, but if you give cinacalcet once a day orally, you then see an increase in BMD…So, transient decreases in PTH may be more beneficial than bringing it down and locking it down.

The results from three large, Phase III trials of cinacalcet were reviewed. In each, patients were titrated, based on efficacy, every three weeks from 30 mg to 180 mg. The results were not presented from the 4-HD study, a six-month extension of 26 patients from the 1-HD and 2HD studies.

- **1-HD Study.** This U.S. and Canadian trial had 410 patients who were titrated, based on efficacy, every three weeks from 30 mg to 180 mg.
- **2-HD Study.** This was a 331-patient study in Europe and Australia, and the dosing again was titrated, based on efficacy, every three weeks from 30 mg to 180 mg.
- **3-HD/PD study.** This was a randomized study of 395 patients in the U.S., Canada and Australia.

Over six months, all three trials reported almost identical efficacy results, and cinacalcet was effective regardless of disease severity. Ca x P was reduced to within KDOQI targets. Serum calcium was reduced to the target range by Week 12 and maintained there. Phosphorus fell by Week 4 and maintained in target. There was a consistent effect on all metabolic endpoints across each Phase III trial. The primary endpoint of iPTH ≤250 was achieved in all the trials within three months, and 90% of the patients did this with a reduction in Ca x P. A researcher concluded, "This suggests you can use cinacalcet as primary therapy."

Calcimimetic	Vitamin D and analogs
Acts on cell surface	Acts on genomic receptor
Inhibits PTH secretion	Inhibits PTH synthesis
Rapid onset (minutes)	Slow onset
Recovery in hours or days	Recovery in days to weeks
Decreases Ca x P product	Increases Ca x P product

Cinacalcet Pooled Safety Analysis

Measurement	Control n=471	Cinacalcet n=665
Mean age	54.8	53.1
Received study drug	100%	99%
Completed Study	78%	71%
Discontinued for adverse events	8%	14%
All adverse events	94%	91%
Serious adverse events	31%	29%
Deaths on study	3 patients	2 patients
Vascular access thrombosis	2 patients	2 patients
Pneumonia	2 patients	2 patients
Sepsis	2 patients	2 patients
Nausea	19%	31%
Vomiting	15%	27%
Diarrhea	20%	21%
Headache	17%	16%
Myalgia	14%	15%
Abdominal pain	14%	12%
Hypocalcemia	1%	4%
Two Consecutive Abnormal Measurements		
Serum calcium <7.5	>1%	5%
Serum calcium ≥ 11.0	20%	7%
Phosphorus ≥ 6.5	60%	47%
Ca x P >55	40%	27%

Cinacalcet 1-HD Study Results

Measurement	Control n=205	Cinacalcet n=205
Baseline Characteristics		
Male	60%	60%
Caucasian	42%	41%
Mean age	54	53
Phosphate binder use	95%	94%
Vitamin D use	68% (decrease permitted)	70% (increase permitted)
Mean iPTH (pg/mL)	651	636
Mean Ca x P	61	62
Results		
Primary endpoint: % patients with iPTH≤250	4%	41%
Secondary endpoint: % of patients with ≥30% reduction in iPTH	11%	6%
Mean reduction in iPTH	Up 10%	Down 40%
Ca x P	No change	Significant reduction
Serum calcium	N/A	Down 6%
Serum phosphorus	Down	Down ~7%
IPTH Response by Change in Vitamin D Status		
Decrease in Vitamin D	+14%	-38%
No change in Vitamin D	+14%	-43%
Increase in Vitamin D	+2%	-46%

BONECARE INTERNATIONAL'S Hectoral (doxercalciferol)

Bone Care officials said the company has 37 sales reps, about half what Abbott has for Zemplar, and doses about $16 million a year in sales. A lower dose of Hectoral and a new indication are both expected to be approved in 2004. An official said, "Abbott will advertise (oral Zemplar), expand the market, and help all of us."

MISCELLANEOUS

Among the interesting findings from abstracts were:

- Two Japanese studies which both found that injection of calcitriol into the parathyroid gland of dialysis patients, who are refractory to IV calcitriol, is safe and effective at lowering PTH.
- A Japanese study which found the efficacy of maxacalcitol is comparable to calcitriol in the effect on PTH metabolism.

CMS ESRD REGULATORY UPDATE

CMS officials attended a session at the ASN meeting to discuss changes in ESRD reimbursement that are going into effect January 1, 2004. The key change that has nephrologists upset is a requirement to see each dialysis patient at least once a month, and preferably once a week. The room was packed, and it turned into more of a gripe and information session.

CMS is starting to pay careful attention to the cost of the ESRD program, which costs the government about $16 billion a year. Dr. Brady Augustine, senior advisor to the Administrator of CMS, told doctors, "CMS has been 'asleep at the wheel' with regard to kidney disease...and we all have to wake up… This program has to change…It won't survive the way it is…I want to be sure Medicare is successful for when I retire and my kids retire…Our goal is to ensure patients receive the most effective and efficient care possible. The opportunities for improvement exist, but in order to achieve them change has to occur…Our belief is that if we can't do disease management in ESRD, we can't do it anywhere…We have more data and homogeneity than anywhere else, and that is why we are pushing so hard to do it in ESRD." Another CMS official said, "A GAO study (found) that 15% of facilities are having problems that could lead to Medicare program termination, with patients at risk. They wanted us to be more strict and close down more dialysis units. They said inspections were inadequate…So, CMS is under pressure to make changes."

CMS is increasingly interested in beneficiaries' outcomes. An official said, "We want to move to…a capitation system…and to do that, some basic tenets need to be in place:

- Case mix adjuster to avoid cherry picking.
- Good safety net of minimum standards.
- Quality incentives."

The change in MCP payment for physicians – a new G Code that goes into effect January 1, 2004 – was the elephant in the room. A CMS official explained why the agency is making this change, "CMS is concerned that some nephrologists are not seeing their patients on a monthly basis, and we are concerned many nephrologists aren't seeing their patients as frequently as they should…If we are going to pay MCP, we want patients seen by the practitioner at least once a month…and we felt that one payment for one visit, another for two visits, another for three visits, etc. (was more appropriate). There is a lot of pressure for us to pay MCP appropriately and to get physicians more involved with patient care…so we challenged the community with the proposed rule…We've gotten a lot of calls from patients who say they haven't seen their doctor in a long time."

Rural doctors will be especially hard hit by this new rule. A CMS official admitted this, saying, "The only thing we couldn't address (in the new rule) is geographic outliers because we didn't have the statutory authority to do that…For rural areas, we are interested in working with the community at things that deal with outcomes, like telemedicine."

However, there were a lot of complaints from nephrologists, particularly rural doctors, at the session:

- Nebraska: "We have no nephrologists in the western part of the state, so we in the east go west…and we will have to reconsider that when reimbursement is cut."
- New Mexico: "We often have to travel by plane, and the proposed fee change will make it far more difficult to do that…Fifty percent of kids are on home dialysis, and the fee schedule has a disincentive for home dialysis."
- Wisconsin: "I am extremely dismayed by this…When I moved to my town, there were 30 patients on dialysis...I now have 85 fistulas… I use PD on a number of patients because I have many patients who travel more than 100 miles each way. To sustain that for a hemodialysis patient is almost impossible…I put a lot of effort into improving my practice and patient lives, and I feel hung out to dry."
- Pediatric nephrologist: "Many centers dialyze at night so kids can go to school, and this rule may have the effect of pulling them back into daytime clinics."
- Washington: "The frequency of visits doesn't necessarily correlate to quality…How will you monitor it?…Seeing patients doesn't mean a quality visit…. I think home dialysis should be (paid) at same level as four visits."

A CMS official warned doctors that complaining about the new rules will stop them from going into effect. He said, "We know payment issues are involved…A lot of facilities have gotten to where they are like an assembly line, in a sense...and that is unfortunate because we really want care to be patient-centered and respect patient preferences…This is a final rule, and it is going into effect."

Other CMS changes include:

- ESRD disease management demonstration. CMS will be moving forward with this July 1, 2004.
- Proposed change in AWP payment. That is on hold because of the Medicare Prescription Drug bill.
- Re-evaluation of EPO payment policy. CMS official said the agency will do that "to be sure it is fair and consistent across the board and up to date with clinical literature on the appropriate epo to give patients."
- Lab test frequency project. Nephrologists are held to different standard than Medicare at large, so the agency is evaluating that.
- Evidence-based guidelines. This is a future change, but CMS is moving toward use of evidence-based guidelines, with a focus on final outcomes -- mortality, morbidity, and quality of life.
- Holding individual dialysis units more accountable.
- Holding networks and SSAs more accountable. CMS plans to issue policy guidance delineating the distinctive roles of networks and SSAs and how they should collaborate and by assessing the results they obtain and publicly reporting those.

Other CMS areas of focus that will be carried over into ESRD in the future include:

1. **Ethnic and racial health disparities.** A CMS official said, "It is interesting that in (the ASN) program, there are a number of papers and posters that relate to this, but when you look at the overall number, they are a distinct minority that deal with this very important area…so there will be a push for more attention on this."
2. **Electronic medical records (EMRs).** A CMS official said, "This has only just started but will explode in the next year as a force in changing the healthcare system. We are discussing a platform that will not only encourage EMRs but perhaps mandate them."
3. **Evidence-based guidelines** and medical policy, particularly with respect to:
   a. Vitamin D, EPO and other medications.
   b. Daily and nocturnal dialysis, where more data is needed to determine policy.
4. **Pay for performance (P4P)**. There are numerous initiatives under consideration to reward providers who meet or exceed certain guidelines

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