Pharmacy and Therapeutics Committee Meeting Record

Date: 9/17/04 **Time:** 9:00 a.m. – 4:00 p.m. **Location:** 3232 Elder Street, Conference Room D **Moderator:** Thomas R. Young, M.D.

Committee Members Present: Thomas R. Young, M.D.; Richard Pines, D.O.; George Pfoertner, M.D.; Catherine Gundlach, PharmD; Jeffery Edwards, M.D., Bob Comstock, RPh; Thomas Rau, M.D.; Rick Sutton, RPh; Cyndy Bunde, P.A, Shawna Kittridge, MHS, RPh; Steve Montamat, M.D.

Agenda Item	Presenter	Outcome/Action
CALL TO ORDER • **Roll Call** • **Reading of Confidentiality Statement** • **Approval of Minutes from July 21, 2004, Meeting** • **Discussion of Key Questions for Upcoming EPC Drug Effectiveness Review Studies**	Thomas R. Young, M.D.	Dr. Young called the roll. All voting members were present. One non- voting member, Mic Markuson, was absent. The confidentiality statement was read by Dr. Young. The minutes from the July 21, 2004, Committee meeting were approved. The key questions for upcoming EPC Drug Effectiveness Review Studies were discussed. These included Newer Antiplatelets; Oral Hypoglycemics; Nonsteroidal Anti-inflammatory Drugs; Proton Pump Inhibitors; Skeletal Muscle Relaxants; Calcium Channel Blockers; Bisphosphonates; and Statins.
DRUG CLASS REVIEW • **Beta Adrenergic Blockers**	Tami Eide, Pharm.D., BCPS, FASHP	Dr. Eide presented information explaining the review of beta adrenergic blockers including indications, how the drugs work, the drug-drug interactions, and availability and dosing. This review included the following drugs: • Acebutolol (Sectral, generics) • Atenolol (Tenormin, generics) • Betaxolol (Kerlone) • Bisoprolol (Zebeta) • Carteolol (Cartrol) • Carvedolol (Coreg) • Labetalol (Normodyne, Trandate, generics) • Metoprolol succinate (Toprol XL) • Metoprolol tartrate (Lopressor, generics) • Nadolol (Corgard) • Penbutolol (Levatol) • Pindolol (Visken) • Propranolol (Inderal, generics, Inderal LA, InnoPran XL) • Timolol (Blocadren)

DRUG CLASS REVIEW • **Angiotensin II Receptor Antagonists**	Tami Eide, Pharm.D., BCPS, FASHP	Dr. Eide presented information explaining the review of angiotensin II receptor antagonists agents including indications, how the drugs work, the drug-drug interactions, and availability and dosing. This review included the following drugs: • Candesartan Cilexetil (Atacand) • Eprosartan Mesylate (Teveten) • Irbesartan (Avapro) • Losartan Potassium (Cozaar) • Olmesartan Medoxomil (Benicar) • Telmisartan (Micardis) Valsartan (Diovan)
REVIEW OF CLINICAL DATA • **Beta Adrenergic Blockers**	Mark Helfand, MD.	Dr. Helfand attended via conference call and presented information explaining the clinical data of beta adrenergic blockers including the study's conclusions. This report was updated in September of 2004. The Committee accessed and reviewed a copy of the information prior to the meeting.
DRUG UTILIZATION REVIEW BOARD REPORT • **Long Acting Opioids**	Chris Owens, PharmD	Dr. Owens presented a report on the Medicaid utilization of Long Acting Opioids and the results of the DUR Intervention.
REVIEW OF CLINICAL DATA • **Angiotensin II Receptor Anatagonists**	Elaine Furmaga, PharmD.	Dr. Furmaga attended via conference call and presented information explaining the clinical data of angiotensin II receptor antagonists drugs including the study's conclusions. This report was updated in September of 2004 The Committee accessed and reviewed a copy of the information prior to the meeting.
PUBLIC COMMENT PERIOD	Thomas R. Young, M.D.	Seven people were listed to speak during the public comment period. Public comment was received from the following: • Dr. DeBruynkops – Forest Labs • Dr. Robert Calder – Mercer • Dr. Derek Terada • Kate Ryan – Astra Zeneca • Dr. Neilann Horner – Glaxo Smith Kline • Dr. John Thomas – no show • An Pham – Reliant Pharmaceuticals • Andrew Weis – Novartis • Ome Ogbru – BMS
COMMITTEE RECOMMENDATION FOR SELECTED THERAPEUTIC CLASSES	Thomas R. Young, M.D.	<u>Beta Blockers</u> The Committee determined that all beta blockers are equally efficacious for hypertension and equally safe. As it relates to a patient with congestive heart failure, there are two agents

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		(metoprolol succinate and carvedolol) and there is no evidence that they are not equally efficacious. Angiotensin II Receptor Antagonists The Committee determined that all the drugs in this class are equally safe. They further determined that Irbesartan has an indication for hypertension with left ventricular hypertrophy to prevent stroke. With respect to congestive heart failure three agents, Lorsartan, Candesartan, Valsartan, have evidence for effectiveness.
SUPPLEMENTAL REBATE INFORMATION *(CLOSED TO PUBLIC)*	Shawna Kittridge, MHS, RPh	Shawna Kittridge presented supplemental rebate information to the Committee members for their review and discussion. This review and discussion were closed to the public.
COMMITTEE FINAL RECOMMENDATION FOR THERAPEUTIC CLASSES	Thomas R. Young, M.D.	Beta Blockers The Committee recommends all generics, Toprol XL and Innopran XL as preferred agents. Coreg will be a preferred agent for use only in congestive heart failure patients. All other agents will require prior authorization. Angiotensin II Receptor Antagonists The Committee recommends Micardis, Cozaar, and Avapro as preferred agents. All other agents will require prior authorization.
ADJOURN COMMITTEE MEETING	Thomas R. Young, M.D.	David made an announcement that Dr. Young is leaving the Idaho Medicaid Program, and has moved to Florida. This is his last P&T meeting. A letter of gratitude from the Governor was presented to him. Dr. W. Terry Gipson, MD, and Psychiatrist will be assuming the role as Medicaid Medical Director and Chair of the P&T Committee. Finally, David announced that Shawna Kittridge will also be leaving the Medicaid Pharmacy Unit to pursue other opportunities. The next groups of drugs to be reviewed by the Pharmacy and Therapeutics Committee on November 19, 2004.

Pharmacy and Therapeutics Committee
Public Comment
September 17, 2004

Dr. DeBruynkops – Forest Labs

Dr. DeBruynkops: Ladies, gentlemen. I'm a family doctor from Idaho Falls. I'm here to talk about: my experience with ARB's in general and Benicar in particular. I have a large solo family practice in Idaho Falls. ARB's have been a very important part of my practice mostly because they are effective and the side effect profile is second to none. For example: almost every other major class that is… such as beta blockers, calcium channel blockers, or ACE's have significant side effects that are not shared by the ARB's. For example: with beta blockers you have central nervous system side effects, you have aggravation of asthmatic conditions; calcium channel blockers are very difficult for me to push to a standard adult dose without side effects of edema and constipation; ACE's, boy I'll tell you are wonderful drugs, they're inexpensive, but the Achilles heel of ACE's is that cough and it is grossly under reported. In my own experience I think it's 20%, of patients get a cough and it's frustrating because the only think I can do is just stop the drug.

Now ARB's for me when they came out were a godsend and it didn't take long to discover that because I don't have side effects like that. The issues of, in particular why Benicar has been useful in my practice, ARB's work and Benicar is not the only ARB that works. I think they are all very effective. In my experience I almost always combine them with a hydrochlorothiazide. They really do work much better. Benicar has a full dose of the ARB and the hydrochlorothiazide is combined into one tablet. It is flat priced. An the side effect profile is excellent with that drug. That makes it very easy for patients to stay on it. The flat price is important and also consistently among the pharmacies in Idaho Falls, it is the least priced. That's important. Now the issue of full dosing with one dose is an important one, and it not shared with the others when used in combination with hydrochlorothiazide. For example, Diovan is wonderful product, if it is combined with hydrochlorothiazide and their full dose of the ARB is 325 mg, but that is not available in the combination with hydrochlorothiazide. So if you want to dose that to the full dose of the ARB and hydrochlorothiazide you're going to have to go to a 160, 12 1/2 , you're talking two pills. That problem is shared with most of the ARB's and I do not have that with Diovan with once a day does and being able to dose both of the individual components in the combination ARB and hydrochlorothiazide has been very useful. But in truth they all work well. But those are the main points I wanted to address to you. I'll be pleased to answer any questions.

Dr. Robert Calder – Merc

Dr. Calder: [Tape paused to check recording]…I've been with Merc for 14 years. Prior to that I was state epidemiologist in Florida, and before that … officer in the Army for a number of years. But my main purpose today is to very briefly present the studies that resulted in the additional indications for Cozaar, the indications for stroke and diabetic neuropathy. An I'm , I personally know many of the authors who did these studies, and in fact I hired one of them, so I'm really representing all of their work to you today. And in doing these studies it takes the best part of ten years to design the study, conduct it, collect the data, analyze the data, publish it, present it

Cozaar regimen, and on the other hand the placebo/regular and usual therapy. But everyone got to about 140 over 90. The mean duration was 3.4 years and the primary input of the study was composite was a double of the …end state renal disease or death and was described this morning. There was 16% relative risk reduction of this composite endpoint that statistically significant. And of the components the doubling of serum … that was significantly reduced by 25% and the progression to end stage renal disease was decreased by 29%, however it was noted previously there was no effect on overall mortality in this study. Secondary endpoints that were significant was a decrease in proteinurin by 34% and a decrease in the rate of decline in GFR by 13%. So as a result of RENAL Cozaar is now indicated in the treatment of diabetic neuropathy in patients with hypertension and …

Turning to the LIFE study.…LIFE was published in the Lancent in March of 2002. it was again a randomized double blind study international study as was RENAL with 9,193 hypertensive patients with ECG documented … The patients were randomized at Cozaar 50 or timolol 50 and increased to 100 of each as needed. And most of the patients ended up taking 100 of each. Actually the mean dose of both Cozaar and… The patients were 54% female, 6% Black. There were two sub-group analyses, one in the 13% diabetic patients and another in the 14% of patients with isolated systolic hypertension. Primary endpoint was again a composite endpoint of CV death, non fatal stroke and non fatal MI. The, there was a 13% reduction in that primary endpoint which was mainly driven by a 25% reduction in the risk of stroke. However, there is no evidence that this benefit applies to Black patients, and that's an important point. Nor does our indication for stroke apply to black patients. There is evidence that the Black patients did not have the same experience as the Caucasian patients in this study, and were not sure why that is. With respect to the diabetic subgroup there was a significant decrease in death due to cardiovascular causes, 37% decrease. There is a all cause mortality decrease of 39% and a 24% decrease in the primary endpoint. That's again in the diabetic subgroup. In the patients with isolate systolic hypertension there was a decrease in both death due to cardiovascular causes as well as all cause mortality. That was 28%. And again as a result of the LIFE study Cozaar is indicated to reduce the risk of stroke in patients with hypertension and … And again with respect to cautionary information, as with all ARB's in the second and third trimester of pregnancy, drugs that act on the rennin angiotensin system can cause injury and even death to the fetus and they should be stopped whenever pregnancy is even suspected.

Again, I hope that you take these studies and the indications that they generated into serious consideration when you deliberate about which drugs are on the list. Thank you.

Dr. Derek Terada

Dr. Terada: Good afternoon. I'm Derek Terada…speaking on behalf of telmisartan and Micardis. As you all know angiotensin receptor blockers have a similar mechanism action. But within the class they differentiate each of the drugs uniquely by the pharmacokinetic and the pharmacodymanic profile. Now with regards to Telmisartan what distinguishes that drug from the rest of the class is basically pharmacokinetics. Telmisartan has probably the longest, it has the longest half life of any agent the class. Document half life for the drug is about 24 hours. The other advantage is the drug is … has a very wide volume of distribution. The other advantage is that Telmisartan has very minimal renal elimination. Less that 1% of the drug actually cleared…through a renal mechanism. So there's really no need for adjustment in patients with mild to moderate … as

Now another thing that has come up in … that has come up recently and may not have been discussed with the Committee is the importance of the fact that there's a very nice study done in the New England Journal of Medicine in 2003 by … of Claumoud and associates. And what they did was look at treated hypertension patients that were followed up at 5 ½ years and look at the importance of ambulatory blood pressure monitoring in these patients and incidents of cardiovascular deaths. And what that study showed when you adjust for traditional cardiovascular risk factors and you also include office blood pressure, ambulatory blood pressure actually was the better predictor than office blood pressure …cardiovascular deaths. ….so what I'd like to point out as far as Telmisartan is concerned, we have on of the largest databases in terms of trials with ambulatory blood pressure monitoring. And so far we have about six double blind randomized placebo control trials and we have four of what we call probe design trials with these randomized blind endpoint trials looking, with ambulatory blood pressure monitoring. Although most of these like I said are short term trials. They don't look at deaths per say, but they look at blood pressure monitoring.

The other thing I'd like to address is the challenge put forth to PHARMA as far as trials are concerned. Currently we have an aggressive …program. We have head to head trials in renal protection …that's an ongoing. We also have the largest cardiovascular trial going on right now called Oncardia which compares telmisartan with an ACE inhibitor ramipril which is the same ACE inhibitor that was used in … study… And we are also looking at the combination if an ACE and ARB is better than an ACE alone. So that would answer a lot of questions. The study is slated to conclude in 2007. We expect data in late 2007 from the trial. So I think in all we have a good product with sustained efficacy. It's proven on short term trials. We have an aggressive program…and I'd like to emphasis that you keep this in mind when you make your decision. Thank you.

Kate Ryan – Astra Zeneca

Dr. Ryan: Chairman, Committee, thank you for your time today. I have just a few bits of information. I have a quick question for the Chairman, I will be presenting information on both Atacand the ARB and Toprol XL the Beta Blocker, would you like me to do them consecutively or…

Dr. Young you can do them both

Dr. Ryan I can do them both, OK. I'll begin with the Atacand to continue on the ARB's. my name is Kate Ryan, I have a Ph. D. in bioengineering, I am a cardiovascular scientist with Astra Zeneca. My past life in academia I worked on receptor binding…

So beginning with Atacand my goal here in the next few minutes is to provide some additional information or clarification from what was already presented and what was excuse me in the drug review paperwork, not to give you a complete picture. I think you already have that. Also, I think y colleagues have a few handouts, that is just if you would like to follow along with a few points. It's really nothing substantial, but it my be there if you want to get back to it. First a few bits of information on Atacand, excuse me Candesartan. It does in the labeling have superiority over Losartan with respect to blood pressure control. This is the only ARB to actually have that. This probably due to its tighter and longer lasting binding to …receptor. There is no …. 450 metabolism, no food interaction. Once daily dosing which was touched on

regards to heart failure. With that I just want to touch on the ... trial and then I'll move on to beta blockers.

I think it was stated in the Committee that you were not seeing the difference between the ARB's and so I want to show you the data is there with heart failure, and it is not the same with the different ARB's. so to essentially overwhelm you with the information from the Charm trial. the Charm trial had three arms in it. Charm added, which would mean Atacand added on top of existing heart failure treatment whether that be ace inhibitors, beta blockers, diuretics, …antagonists. Then there was the Charm alternative trial to those that were intolerant of an ace inhibitor. And finally the Charm preserved trial which is a unique heart failure patient population. Those with preserved left ventricular dysfunction. So they actually have ejection … greater than 40. this is a previously unstudied patient population. So that is the Charm program. Three completely separate trials. They are parallel trials, independent, randomized, double blind, placebo controlled in three distinct patient populations. The Charm program and the overall trial combines information from the three trials. It was set up to be that way. So it's essentially four trials you could look at. One is combining the results of the overall, the other in the three patient populations I just described. So it is very important to realize that including that one is very unstudied patient population which we in medicine need to find out more about, patients with and ejection factor of greater than 40 but with heart failure.

So with that just, I'm not going through each of the slide, I'm going to Charm overall program. Just to show you the primary endpoint in each of the trials of Charm is stated on page … primary outcome for … trial CV death or heart failure hospitalization. So, the overall program, for those of you without the handout just to remind you of the numbers, the added trial to this would be beta blocker, ace inhibitor, diuretic and possibly an…antagonist. You have a 15% reduction in the primary endpoint of CV death or heart failure hospitalization. The alternative arm that would be in those that were intolerant to an ACE inhibitor you have a 23% reduction, also significant. In the preserved, again being those with preserved left ventricular function. You… have non-significant, but you do have and 11% decrease in the primary endpoint of CV death and heart failure hospitalization. When you combine these, the overall, you actually have a 16% decrease in the primary endpoint. It's obvious from the numbers from the chart that the 3rd trial, the preserved arm does bring the numbers down a bit. Remember this is a very distinct patient population that …we might not have more information for. To really hit home with that is to say that we at Astra Zeneca filed for an SNDA for heart failure in all three indications. Added, alternative, and in those with preserved left ventricular dysfunction, function excuse me. And the FDA has granted fast track in the added on. Especially in light of these results being directly contradictory to those in the …trial where Charm suggesting the combination of all of them should result in an additional 15% reduction. Finally with regards to Atacand, the last slide, I just want to emphasize that in the overall program you can actually breakdown the subgroups and you can see that in the three Charm trials even though a distinct and unique patient populations, that Atacand is effective at reducing CV death and hospitalization for heart failure regardless of the subgroup. Being diabetic, hypertensive, with or without ACE inhibitors, with or without beta blockers, with or without…antagonists. Any questions on Atacand.

Dr. Young You have two minutes.

should not have been studied. One of the many reasons dosing regimen was very unequal in the Comma trial as well. I could provide you that data if you request it. Finally, I provided you with some charts on the pharmacokinetics and pharmacodymamics if you have any questions with regards to these two formulations, the immediate release …your addressing the extended release the Toprol XL, Toprol … Thank you, may I entertain any questions.

Dr. Young Clarification question. Was, is the material that was submitted to us for review, was it submitted in a dossier form to the EPC for review, so all this has been reviewed by the EPC.

Dr. Ryan I believe so.

Dr. Young I would strongly encourage, the process is to not deliver information at the last minute. It's to make sure the EPC process is the information goes to them, they do the evaluation, because we have no way of stopping the process to evaluate the value and validity of the information provided it's about studies. If the studies have been studied, it makes sense and puts everyone on a level playing field. Okay. So please if you bring this information, please tell us if it either was or was not included in your dossier. And if it was not include in your dossier we strongly encourage you to maintain the validity of the process. Which is give us all the information so that we have an opportunity to review it, evaluate its validity, its scientific support, and it's presented and then you can leg off of that. So was this …

Gallery Member …this was presented to the Committee, to Tyler last we and we were advised we could present here to you today.

Dr. Young Simple question, was this information we were provided here today, provided in your dossier to the EPC?

Gallery Member I believe it was.

Dr. Ryan I believe it was, yes.

Dr. Neilann Horner – Glaxo Smith Kline

Dr. Horner: Thank you. I'm Dr. Neilann Horner with Glaxo Smith Kline, I'm here to talk to you about Coreg. And what I hope to do is just pull out the specifically what the differentiations for the product, and I'd be glad to entertain any of the questions you may have on some of the discussion was of interest when spoke earlier about Carvedilol- Coreg.

First of all thanks so much for the opportunity to speak today and also to Mark and his group. An outstanding document. It's been needed for some time and allows us to have some good scientific discussion, putting all the evidence in once spot, super helpful.

My comments at this point is to Coreg. It is unique in that it blocks beta one and beta two and has some alpha one activity so your comment about why would someone possibly tolerate one drug or the other, there are some significant chemical differences between the products. Additionally Carvedilol is known to have neutral metabolic effects and we are actually studying extensively how clinically relevant even some positive component might be although that is not

There was a little concern raised they didn't indicate class 3, class 4 New York heart association, however the language in that paper is identical to what class 3, class 4 is and that is symptoms with mild or at rest, so that is essentially class 3 or 4 at that point. A large trial and probably the only other evidence available for any of the other agents approved with evidence for heart failure was Merik that I could find, and that was a subset of 139 out of 3,991 patients, 69 of which would be on meds. A post … analysis that were comparing to a 2,200 person trial. So the severe class, the sever heart failure evidence is unique to Carvedilol. At least in its strength of robust evidence.

The fourth point I'd like to make is that Coreg has been approve to reduce mortality in the US. And to draw your attention to the EPC report that it raises concern about how relevant the Merik HF information is to the US population may require a little bit more attention. As far as efficacy in real world, the …registry offers a little bit of additional information where we looked at folks randomized in prospectively 12 months after starting Carvedilol and looked at them 12 months before. Uh, a 41% reduction hospitalization, 61%, that's overall hospitalization, 61% decrease in heart failure hospitalizations specifically, and an 8% increase in all other hospitalization, that could be related to a phenomenon such as people still being around if you will. And this is in 4,280 folks. So starting gather some relevant information to pairs and so on at that point. It is my intention to point out a few unique components of Carvedilol, it is a very well studied drug in an environment where there is a lack of head-to-head comparisons, I think it's important to realize the robust nature of the multiple large scale randomized, prospective clinical trials is worth something when we are offering care to patients where there's a huge opportunity for prevention. 5 million people in this county with heart failure. About 1.2 million post….

Those are my comments. I'll entertain any questions I can clarify for you.

<u>An Pham – Reliant Pharmaceuticals</u>

Mr. Pham: My name is An Pham from…Reliant Pharmaceuticals. I want to thank the P&T Committee for the opportunity to provide some public comment on the clinical benefit of a unique drug delivery system for Propranolol or InnoPran XL. InnoPran XL is an innovative formulation of Propranolol following the landmark result of beta blocker heart attack or BHAK trail data in which Propranolol demonstrates significant reduction in morning peak incident of certain cardiac death compared to placebo and a significantly …reduction in mortality in patient with heart attack, recent heart attack or post MI. To … InnoPran XL employed … and delayed onset and controlled release technology that produced ….formulation of Propranolol. The capsule contained two things. Contained a sustained release … and also a delay onset as well. The result of the is a consistency in blood pressure control, 24 hour blood pressure and heart rate control. Presently, InnoPran XL is indicated for the management of hypertension, to be taken at 10 pm possibly 10 pm or at bedtime. There is no generic equivalent of long acting Propranolol for either ….or InnoPran XL.

In summary I would strongly ask the P&T Committee to recommend the InnoPran XL to be on the Idaho State preferred drug list or formulary for the following …consideration. First, …approach on hypertensive treatment with pm dose and am peak effect. Second, important therapeutic benefit for patient to decrease morbidity and mortality from morning cardio vascular events. And lastly, the said pm and …side effects. I know there was a comment earlier about

Mr. Weis: Excuse me, my wife insisted on getting a cat so I'm just getting over my allergies. I'd like to address some data specifically that were to included in the EPC report which was a recently published a clinical trial called VALU which addresses Valsartan a first modern ARB used against third generation calcium channel blocker in … hypertension. This was a patient population studied of over 15,000 patients …dose pectration schedule was an electo-titration schedule was not a forced titration schedule. It used some older dosing and some older labeling that is consistent with a number of the European labels that we see. At the end of the trial there was no significant difference between cardiovascular morbidity and mortality between Amlodipine and Valsartan. There are similar reductions in blood pressure. Now even with this older dosing, once again, with this dosing one of the things we saw was there was not a primary/secondary endpoint we saw a 23% reduction new onset diabetes. Now this was not a first finding for an ARB but it is certainly suggestive of some additional clinical trial work that we are going to be doing. Which again …trial which it titled Navigator which will look at Starlix and Diovan in exploring the effect of diabetes and potential protective effect of an ARB. In terms of addressing some of the data about high risk hypertension patients, the Valu trial patient inclusion criteria were those patient considered high risk based on successor JNC statements with respect to risk factors and existing disease states. So the highest patients were implicit in this Value trial. I'd also like to address a point that was made in the VALPAC trial, specifically in congestive heart failure, this trial was not powered to achieve superiority, it was powered instead to look at equivalency to existing gold standard therapy of captopril. Accordingly, our indication reads that we are indicated for patients in heart failure or intolerant … therapy. This gives you another agent to look at when patients are intolerant of that gold standard therapy in an ACE inhibitor. I'd also like to mention that less than 50% of heart failure patients are already on an ACE inhibitor. So this gives you an alternative for that. And I'd like to entertain any questions you may have.

Committer Mbr why wasn't' that data included?

Weis Valu was published right after the time horizon which the literature search took place, it was only published in the last couple of months so it would be included in the literature search that Dr … did in the … exam.

Dr. Young Hey Mark, so that study will be included in the next review?

Dr. Helfand Yes, Novartus has made a commentary on our report when it was up for public review on the website, and our response to that was just that, the results of the Value trial, this was by the way a huge trial of high risk, hypertensive patients, that they'll be included in the next review. And it was Valsartan versus Amlodipine as the speaker said. Uhm, so that's right.

Dr. Young Do you have any comments for us at this point about that trial.

Dr. Helfand I'm not sure what kind of comments to make.

Dr Young I mean … were there any changes to the report as a result of those comments by Novartus.

Dr. Helfand No, the conclusion that the authors in the report came to was the study would be included in the next report and there wasn't' any reason to change this version against the usual policy, to

So if you could look at some of the data that compares Irbesartan versus Valsartan versus Losartan and some of the other ARB's at least it could yield some thoughts or some insight into some differences between these ARB's. and the second one, I wasn't here this morning but I understand there may have been some confusion on the IDNT study and the groups that were included in that study. And specifically there were three groups in IDNT. There was a placebo group, there was an Almodipine arm and then there was an Irbesartan arm. And what that study essentially showed, that even with equivalent blood pressure control, Irbesartan was better at reducing a combined endpoint of…time to end stage renal disease, an increase in … clearance. There was no death, there was no, there was, the endpoint of death was not specifically looked at and there was no significant difference in that endpoint or heart failure endpoints or cardiac mortality. And a lot of that has to do with the size of the study. Because there were three arms in the study and that reduced the abilyt to find a significant difference. And if the committee has any questions, I'll gladly answer them.