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Recommendations:

This memo will summarize this reviewer's rationale for approving Natrecor (Nesiritide) for the treatment of an acute exacerbation of CHF. This approval, however, is not made with much enthusiasm. I've appended my suggestions for labeling as Appendix A.

No additional subjects have been enrolled into Natrecor's clinical trials since the submission of this NDA. No safety update is, therefore, anticipated. DSI audits have been performed. One final report on these DSI audits is still outstanding. Facilities inspections are all completed, but the report concerning the Scios facility is still not available. With respect to the microbiology, the data supporting the integrity of the container closures integrity test was considered suboptimal. Rectifying this deficiency does not appear an insurmountable obstacle to approval.

The database for Natrecor is marginal. Natrecor, however, could be approved at a single infusion regimen (consisting of a bolus of 0.03 ug/kg followed by a constant infusion of 0.015 ug/kg/min) in a population of stable congestive heart failure patients who suffered an acute exacerbation of their disease. Higher doses (bolus plus infusion) were not convincingly more beneficial than the lower doses, but had more episodes of hypotension and these episodes were of longer duration and of greater intensity than those in the lower dose group.

Retrospectively, lower doses of Natrecor should have been studied more extensively in the target population. Doses as low as 0.003 ug/kg/min, infused for durations too short to establish steady state response, decrease PCWP in patients with stable CHF. Longer infusion times would likely have shown greater effects on wedge pressures. Cardiac indices, at this low infusion rate, during this short period of infusion were not convincingly increased. Somewhere in the dose range between 0.003 and the 0.015 ug/kg/min infusion rates (with the corresponding bolus dose) lies the reasonable starting dose that optimizes hemodynamics (wedge pressure and cardiac index) and minimizes adverse events (hypotension).

Instructions for optimizing doses are problematic and for this reason I've recommended only a single infusion regimen (with bolus) be approved. It would be difficult to construct data-derived recommendations that the patient should be titrated to the desired effect. There is little empirical data which support the safety of titration schemes. There were only a small number of subjects who were titrated to higher doses during the clinical trials (see Tables Global-17 and 18). Nearly all subjects who were upwardly titrated had their dose decreased or discontinuing at some previous time, so these patients weren't titrated to attain a hemodynamic effect but were titrated to the pre-stipulated dose.

Instructions for up-titration also cannot be made based on the current state of knowledge of the relationship between kinetics and dynamics of Natrecor. The terminal half-life of Natrecor is approximately 20 minutes. The time course for its onset and offset effects for PCWP appear to be governed by much longer time constants. Blood pressure response also appears to be governed by longer time constants, which may or may not be similar to those governing PCWP. Overexuberant upward titration of Natrecor, in order to rapidly optimize hemodynamic responses (PCWP), would not only likely overshoot the goal wedge pressure but would also result in excessive hypotension. Absent an adequate empirical data base there appears to be some risk in recommending an untried titration scheme.

This long dynamic half-life of Natrecor coupled with what appears to be substantial hypotensive effects at the recommended infusion regimen, has implications with respect to adding Natrecor to concurrent therapies, particularly any therapies that also act through vasodilation. Although there is some experience (modest) in adding vasodilators (or for that matter inotropic drug) to Natrecor, there is no experience with adding Natrecor to stable regimens of other medications. During clinical trials all inotropes and vasodilators were discontinued before starting Natrecor infusions. The consequence of adding Natrecor

to ongoing therapies is that hypotension, slow in onset, severe in intensity and prolonged in duration is a likely consequence. Back titration off of Natrecor would not rapidly reverse the excesses in hypotension.

I have no reason to believe that Natrecor is better than other treatment for acute exacerbation of CHF, it may or may not be inferior. Natrecor, however, does not have to be superior to other treatments; only superior to placebo. In patients with CHF, Natrecor decreases pulmonary capillary wedge pressures (PCWP) to a greater extent than placebo. There is also some data, admittedly flawed, and by itself, not sufficient to allow a claim in labeling, that suggests that Natrecor's hemodynamic effects lead to short-term improvement relative to placebo in signs/symptom of acute decompensated CHF .

The adverse event profile of Natrecor is far from benign. Those adverse events, such as hypotension, which appear to be an extension of the pharmacological actions of Natrecor are only of concern because of the long duration of Natrecor's action and the long time that is required to reverse these effects. The frequency and intensity of hypotensive episodes is substantially diminished at the lower infusion rate of Natrecor infusion. This lower rate offers the best balance of benefit and excessive blood pressure decreases.

Natrecor is associated modest deterioration of renal function. More patients sustained modest increases in serum creatinine when compared to the placebo/standard (#704.325) or standard care groups (#704.326). To a large extent these increases in creatinine reversed over time (See Dr. Throckmorton's review). Creatinine increases, however, may be a natural consequence of afterload reduction. Few of those who were enrolled in the control group in study #304.726 were treated with afterload reducers (nitroglycerine or sodium nitroprusside); most were treated with inotropic drugs. The difference in prevalence of renal dysfunction between control and Natrecor treatment might merely be a reflection of the difference in the mechanism of action of the drugs which were used in the standard therapy group. Given the largely reversible nature (at least with respect to serum creatinine) of the renal impairment with Natrecor, this adverse event should not be an impediment to the approval of Natrecor.

Natrecor should be labeled for use only for the population who has sustained an acute decompensation of stable congestive heart failure. The labeling should make it clear that the safety and efficacy of the use of Natrecor in subjects whose congestive heart failure is the result of an acute myocardial infarction has not been studied.

I am neither comforted nor worried by the mortality outcomes or the time of hospitalization or rehospitalization rates during the development program. Only a modest number of subjects were enrolled, the duration of treatment was short, concurrent treatments were allowed after a short observation period, so it not surprising that little differences were observed in these events. We have not in the past required that a drug demonstrate an improvement in either morbidity or mortality in a developmental program for acute exacerbation of stable CHF. I see no reason that Natrecor should be held to a different standard. Natrecor does not increase urine output or sodium excretion in a CHF population, despite favorable hemodynamic effects on wedge pressure and cardiac output.

Additional Points:

Only a few main new points, not emphasized in Dr. Throckmorton's review, will be covered in this memo. The rest of this document summarizes key points of the safety and efficacy of Natrecor. Dr. Throckmorton's review contains excellent and comprehensive discussions on both the efficacy and safety of Natrecor. Dr. Papoian's and Dr. Sadrieh's reviews are excellent sources for the pharmacology and biopharmaceutical studies, respectively, that were submitted by Scios for Natrecor. Dr. Raymond Miller, of the Agency, confirmed the sponsor's PK-PD analysis of the data from the steady state portion of study #704.307. This analysis was included in Dr. Sadrieh's review. Dr. Moore, of HFD-510, reviewed the

chemistry as well as the manufacturing and controls of this peptide. His review and subsequent discussions were most helpful in placing the two methods of hBNP production, which were used during the development program into some contextual framework.

The three additional points are:

1. The pharmacodynamic effects of Natrecor are not optimal for its proposed use. The time course for the onset and offset dynamic effects of Natrecor with respect to PCWP, appear to be relatively slow. The onset of blood pressure effects are also slow, with a time course which may or may not be the same as for wedge pressures. Once the physician chooses a dose of Natrecor, the effects of the drug, both on wedge pressure and also on blood pressure, progress until dynamic steady state is reached at approximately 4-6 hours of infusion. The physician must be cautious not to aggressively increase the infusion rate; otherwise the goal wedge pressure will be overshot and blood pressures will be excessively dropped. Once a patient becomes hypotensive, decreasing the Natrecor dose is only slowly followed by the reversal of both the PCWP and BP effects.

2. The sponsor implies that Natrecor acutely (after 6 hours of infusion) improves the signs and symptoms of acutely decompensated. This benefit is only supported by a single placebo-controlled study (study #704.325). The study, which supports symptomatic benefit is, however, flawed. Blinding during study #703.325 was maintained only for the first six hours of the infusion protocols. Although the timing of the symptom assessment occurred during the blinded portion of the study, the data was not locked-in while the investigator was blinded. When the on-therapy symptom assessments were committed to the CRF, the investigator was already unblinded as to treatment, that is, whether the subject received placebo or Natrecor. Data collected during this study was not always contemporaneously transcribed to the CRFs. ADRs, which occurred later in time, were occasionally listed above earlier ADRs on the CRF. Medications were occasionally also recorded out of time sequence. It is, therefore, not possible to be certain which information, including symptom benefit was committed to the CRFs in a timely manner. If this data was transcribed after unblinding of the dose, symptom assessment should be treated as an open-labeled assessment.

The dose of Natrecor, however, was not divulged to the investigator when the blind was broken in study # 704.325, nor was the dose divulged during open-labeled treatment during study # 704.326. No dose-related benefit to symptom improvement, however, was discerned in either study.

The investigator who performed the hemodynamic measurements during both studies #704.325 and #704.326 also participated in the symptom assessment. Not only did this investigator complete the investigator's assessment, but the investigator also aided the patient in completing the patient's assessment. There was, therefore, the potential of cross-contamination between hemodynamics and all metrics of symptom improvement. Hemodynamic measurements and symptoms cannot, therefore, be considered independent outcomes.

Lastly, the six point patient questionnaire was not validated as a useful instrument for use during acute decompensated heart failure. Nevertheless, many of the questions are so straightforward and related to acute symptomatic decompensated heart failure, that it would be difficult to argue against the questionnaire's relevance.

Aside from the issue of blinding, each of the pivotal studies had deviations from optimum study design[1].

[1] Deviations:

Studies #704.311, #704.325 and to some extent #704.326 were all tainted by systematic errors. It is likely that that PCWP and other hemodynamic assessments are sufficiently robust so that it is unlikely that additional analyses would alter the conclusions. For other analyses, statistical significance may be lost but overall direction of effect is unlikely to be changed.

Study 704.311

A. With respect to study 704.311, the original protocol proposed the enrollment of 80 patients or 20/group. The final enrollment, however, was 103 subjects. The reason supplied by the sponsor for enrolling these additional subjects was that several subjects were given the wrong medication dose because of a pharmacy error. These subjects were replaced. The sponsor became aware of the mistaken doses when a monitor was dispatched to the study sites and discovered that the pharmacist incorrectly formulated the infusions. This monitor, according to the sponsor was unaware of hemodynamic outcomes. However, since placebo patients were only given D5W, no placebo patients could be misdosed and excluded. All exclusions were, therefore derived from one of the active treatment doses. The original protocol made no provisions for replacing subjects who received the wrong dose. Furthermore, the CRFs contained no information as to how the infusions were formulated. Reviewers could, therefore, not independently verify that patients were mis-dosed.

The sponsor, moreover, performed several (two) interim looks but claimed the intent was to plan future studies and not to terminate the ongoing study. No statistical penalty was assessed despite changing the size of the study while it was ongoing. It appeared possible that the interim looks, if positive, could have dictated that the study be completed after the 80 enrolled patients (or slightly more patients, if the size of the study was predicated on enrolling 20 patients /group).

In order to see if the early termination biased the interpretation of the study, Dr. Cui, our statistician performed an analysis limited to the first 80 subjects who were enrolled. Those who had values missing were assumed as worst case outcomes (see point C). The study results did not materially change in limiting the analysis to the first eight patients.

B. Patients were randomized before the Swan-Ganz was inserted and before the hemodynamics defined the patient as eligible. If the patient could not be instrumented, had ineligible measurements or became unstable, the patient was discontinued and considered as never enrolled.

C. Although the sponsor labels the analysis as "intent-to treat", those patients who did not have readings within the appropriate time frame were excluded (many of these patients could have had readings missed because they discontinued due to ADRs or due to worsening CHF). There were a total of 6 patients who were not included in the sponsor-labeled "intent-to-treat" analysis.

D. The pharmacist on-site was unblinded as to treatment.

E. The control group was not a true placebo because the bolus and infusion of placebo was D5W. No "placebo" vials were supplied. To the extent that the physical characteristics of the Natrecor solution looked different from D5W, the physician could be aware of the treatment.

F. The p-values were not corrected for multiple primary endpoints. Two primary endpoints were pre-specified in the original protocol. The first was the absolute change in PCWP at 3 hours and the second the absolute change in PCWP at 24 hours.

G. With respect to secondary endpoints, there were a total of two time points and four hemodynamic measurements. No prespecified analysis for the multiplicity of end points was stipulated.

Study 704.325

A. With respect to study 704.325, the pharmacist on site was unblinded as to treatment.

B. The control placebo group was not a true placebo because the bolus and infusion of placebo lacked any excipients. To the extent that the physical characteristics of the bolus or the infusion differed from D_5W, the physician could be aware of the treatment.

C. As noted above, blinding of the study was only for the first six hours. The blind was to be broken only after the 6-hour readings and after the 6- hour symptoms were collected. To break the blind, the investigator phoned the central randomization center and received information as to treatment (placebo or Natrecor, but if on Natrecor, the dose was not divulged). The investigator received a dated and timed fax that indicating the date and time that the blind was broken. The problem, however, is that although the timing of unblinding was such that the data was already collected, it was quite clear that there was no requirement that the data had to be locked in. In fact, it is quite clear that the data for some parts of the CRF was collected and only later transcribed to the CRF. For example, listing of concurrent medications and adverse events were not always done in a strictly chronologic order and therefore, must have been organized prior to committing the information to the CRFs. We have asked DSI to clarify whether there were contemporaneous nursing notes, which verify that the transcribed information was indeed accurate.

D. It appears that the symptom assessments were collected by the investigator who could be aware of the results of the hemodynamic measurements. Moreover, the instructions on the CRFs for the collecting the patient's symptoms and change of symptoms were that they were to be performed by the Investigator in conjunction with the patient. Even the patient's symptomatic assessment was cross-contaminated by someone who could be aware of the hemodynamic response.

E. The sponsor treated those who discontinued, because of need for additional therapy, as "worst outcomes'. If a subject discontinued because of and adverse event, however, the subject was not listed as an "worst outcome", but apparently was censored from the analysis. It might be reasonable to censor those who had adverse events but required no additional inotropic or vasodilator support. Those however, that required some additional treatment do not in my mind differ from those who required additional other medications.

Study 704.326

A The study was labeled as unblinded with respect to the standard therapy regimens.

3. Two methods of preparation of Natrecor were used in the 3 pivotal studies. In order to approve Natrecor, the data for all studies need be combined (see Chemistry).

Background

The basic science of Natrecor (hBNP; Nesiritide) is derived almost entirely from publications. The underlying data was not available to our reviewers for critical analysis. The basic science of Natrecor, will therefore, only be summarized. I have appended a relatively recent review article[2] as Appendix B.

There are three members to the class of natriuretic peptides: A-type, B-type and C-type. Each natriuretic peptide is encoded as a prohormone by a unique gene. A-type natriuretic peptide is predominantly produced in the cardiac atria. Increased wall tension, that reflects an increase in vascular volume, is the primary stimulus for its release. Other factors such as endothelin, arginine vasopressin and catecholamines, are also stimuli for A-type natriuretic peptide release.

B-type natriuretic peptide (abbreviated either as BNP or hBNP, if derived from human sources) is elevated in patients with CHF and ventricular hypertrophy, and is predominately produced in cardiac ventricles. C-type natriuretic peptide comes in one of two lengths either 22 or 53 amino acids. These two peptides are produced by digestion of the same precursor peptide but at different sites. The 22 amino acid form is the more active form and predominates in the in the CNS, anterior pituitary, kidney and vascular endothelial cells.

Three receptors, which bind hBNP, have been identified. Two of these receptors are most important in describing the effects of hBNP. One of these receptors, guanalylyl cyclase receptor–A (GC-A receptor), is activated upon binding either the natriuretic peptides A or B, resulting in increases in intracellular cGMP. Binding constants were measured for natriuretic peptides to constructs of this receptor, the extracellular domain of the guanylyl cyclase receptor, which was fused to the constant domain of the IgG molecule. ANP, as judged by displacement of ^{125}I-hANP (dissociation constant of 1.9 pM), was more potent than BNP (dissociation constant of 7.3 pM) [3] for this hybrid receptor.

When either ANP or hBNP is infused into normal humans, so that plasma concentrations were approximately 30-40 pM (or 5-20 times than the dissociation constants), plasma cGMP was approximately 40-50% higher during the ANP infusion than during the hBNP infusion. If one subtracts baseline cGMP concentrations, the effect on cGMP generation were approximately 3-fold greater with ANP than with hBNP (see Figure Global-1). In summary, the effects of ANP appear to be more important than hBNP (in normals), based both on dissociation constants as well as what appears to be maximal effects in increasing plasma cGMP.

Natriuretic peptide receptor C appears to be important for clearing all three natriuretic peptides. Natriuretic peptides bind to this receptor and are internalized and subsequently degraded. Circulating h-BNP is also cleared by neutral endopeptidases.

B. The pharmacist on site was aware as to the dose of Natrecor treatment.

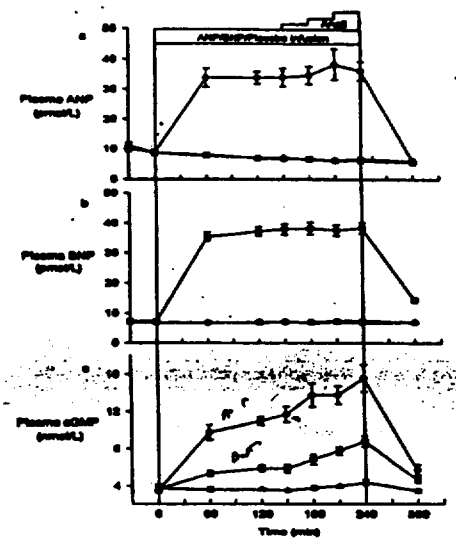
C. The same physician filled out the hemodynamic measurements and the symptomatic benefit forms.

[2] Levin ER; Gardner DG; Samson WK; "Natriuretic Peptides"; 1998; New Engl J. Med 339:5 321-328.
[3] Bennet BD; Bennet GL; Vitangcol,RV; Jewett JRS; Burnier J; Henzel,W; Lowe,DG" Extracellular Domain-IgG Fusion Proteins for Three Human Natriuretic Peptide Receptors". J Biol Chem 1991: 266:23060-23067.

The mechanisms by which natriuretic peptides might be useful in improving cardiovascular function are summarized in the attached article. ANP and presumably hBNP decreases preload and afterload by decreasing blood pressure and peripheral vascular resistance. The proposed mechanisms of hBNP's effect include: direct arterial dilation, decreased capacitance vessel resistance, and shifts of fluids into extravascular spaces. Natriuretic peptides also may induce natriuresis (reviewer's comment: at least in normals) as well as a diuresis by direct effects on the kidney and/or the renal vasculature. hBNP may also reduce sympathetic tone by dampening baroreceptors (by suppressing release of catecholamines and/or by a suppressing sympathetic outflow from the central nervous system and/or by lowering the activation threshold of vagal afferents).

I did not see any data that addresses whether the vasodilator effects of hBNP are uniform across all vasculature beds or whether there is preferential vasodilatation of only some beds. I did not see data which describes the distribution of GC-A receptors within each vascular bed.

Figure Global-1[4]



Chemistry:

Natrecor is a 32-amino acid peptide that was synthesized by two different methodologies. Natrecor, that was used in two of the three pivotal studies [most of those in #704.325 (69/85 treated patients) and all treated patients in study #704.326] was synthesized a recombinant methodology. Natrecor will be synthesized commercially by this method. The preparation used in most of the other studies including #704.307 and #704.311was synthesized by the peptide synthesis method.

Natrecor as produced by either method was indentified as the same molecular species by the following methods: amino-terminal sequencing, electrospray mass spectroscopy (mass ion), optical rotation and co-elution of recombinant with reference synthetic standard. In addition to the chemical determination, a biological assay that measured an ED50 of cGMP production when hBNP was incubated with CHOGCA5A1S cells, was required to define the entity as hBNP. The CHOGCA5A1S cell line is a

[4] Hunt, PJ; Espiner, EA, Nicholls,MG; Richards, AM; Yandle, TG "Differeing Biological Effects of Equimolar Atrial and Brain Natriuretic Peptide Infusion in Normal Man". ; J Clin Endocrin and Metab 81 3871-3876, 1986.

modification of Chinese hamster ovary cell lines (CHO-K1) that was bio-engineered to over-express the human GC-A receptor. Although the specification range for acceptability of the bioassay was broad (50-150%), this assay, nevertheless, assures that the synthesized material is active peptide.

The upper limit of structurally related impurities was to be %. The impurity profile, of the two preparations, however, differed. It is not a requirement to define the biological activity of the impurities; consequently, it is not surprising that no information about their activity is available.

Based on discussions with Dr. Moore, the consulting chemist the quality of the manufacturing controls for Natrecor was more than adequate for this class of peptide drug.

Despite what appears to be strong evidence that the two preparations result in the same bioactive material, there is some kinetic and dynamic information derived from animal studies which suggests that the synthetic and recombinant preparations act differently. Human kinetic and dynamic data, however, show that the two preparations act similarly, though the confidence intervals are wide.

When administered to rabbits (n=6/group), the kinetic profile the two Natrecor preparations differed (see Table 10 p.80 of Dr. Papoian's review; summarized in Table Global-1). Clearance for the recombinant hBNP was only 68% and 80%, at the 30 and 10 ug/kg bolus doses, comparing the recombinant to the synthetic material, respectively. The corresponding AUC for the recombinant compared to the synthetic forms was 48% and 38% higher at the 30 and 10 ug/kg bolus, respectively. Similar effects were seen in monkeys after two weeks of steady state infusion (See Table 8 of Dr. Papoian's review, p 63).

Table Global-1: Kinetic Comparisons between the Synthetic and Recombinant Preparations.

Dose	Animal	Method of Administration	Parameter	Formulation	Units	Measurement mean ± stdev
10 ug/kg	Rabbit (n=6)	Bolus	AUC 0-90	Recombinant	ng.min/ml	480 ± 101
10 ug/kg	Rabbit (n=6)	Bolus	AUC 0-90	Synthetic	ng.min/ml	348 ± 46
30 ug/kg	Rabbit (n=6)	Bolus	AUC 0-90	Recombinant	ng.min/ml	1262 ± 396
30 ug/kg	Rabbit (n=6)	Bolus	AUC 0-90	Synthetic	ng.min/ml	858 ± 146
1.0 ug/kg/min	Monkey (4M + 4F)	Infusion	[Conc]	Recombinant	ng/ml	59.80 M=52.7 ± 11.6 F= 66.88 ± 5.1
1.0 ug/kg/min	Monkey (4M + 4F)	Infusion	[Conc]	Synthetic	ng/ml	44.52 M=46.6 ± 19.0 F= 42.8 ± 28.2

With respect to the kinetic comparison in humans, those enrolled into study #704.325 received either the synthetic preparation (those who enrolled early; n=14) or the recombinant product (those who subsequently enrolled, n=51). In comparing the synthetic to the recombinant preparations, the clearance of Natrecor was equivalent (recombinant product clearance = 8.50 ml/kg/min; 95% CI 7.40 to 9.60; synthetic product clearance = 8.54 ml/kg/min; 95 % CI=7.04 to 10.05). The confidence intervals, however, are large and substantial differences in clearance are still possible.

With respect to a comparison of the dynamic effects of the two preparations, there are one or two *in vivo* or *in vitro* studies, which appear to show some differences in the activity of Natrecor when comparing the synthetic to the recombinant material. In Figure 41 of Dr. Papoian's review (reproduced as Figure Global –2), the blood pressure drop of rabbits appears to be greater with the recombinant formulation relative to the synthetic formulation. This difference remains despite the nearly order of magnitude range of doses that were studied. The differences, if they are real, may be related to impurities that trail along with the hBNP since the maximal effect of hBNP is apparently reached.

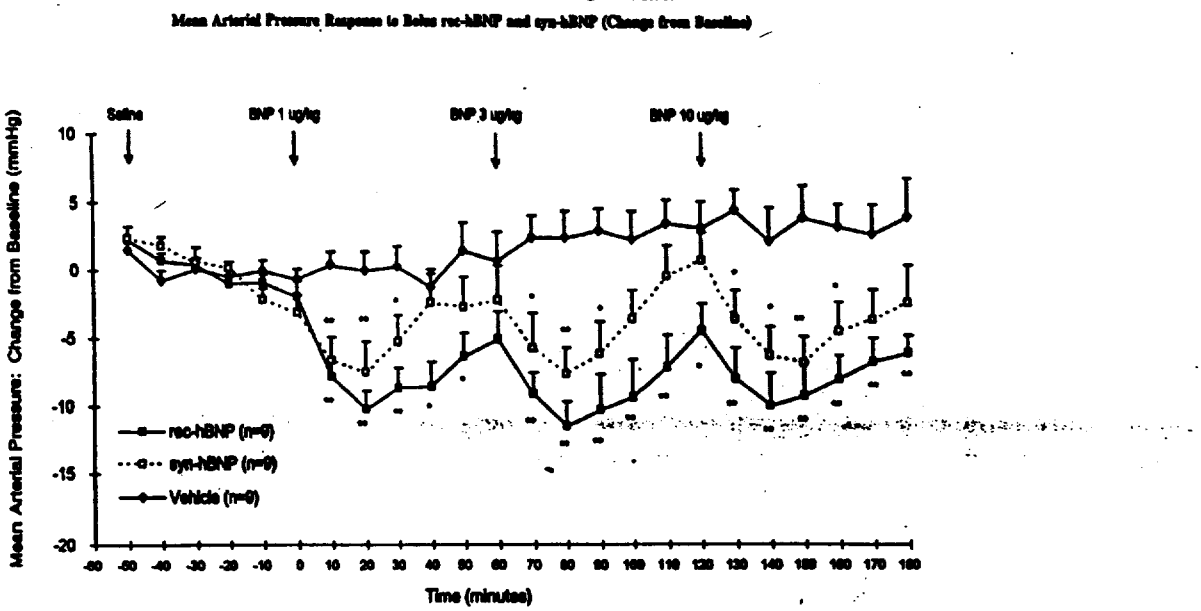
I've analyzed and compared the effects of the 16 patients in study #704.325 who received the synthetic preparation, and compared the effect in these subjects to the entire treated population. The effects of PCWP appear to be similar, but the confidence intervals for these measurements in the 16 patients (8 in

each of the 0.015 and 0.030 ug/kg/min infusion regimens) are quite large (see Table Global-7). There were similar effects in decreasing mean arterial blood pressure for the high dose infusion –8.8 mm Hg versus a median change of –8.4 mm Hg (total versus synthetic cohort). For the low dose infusion group, there was a lesser mean effect of the synthetic preparation +0.38 mm Hg versus the median effect for the total group –4.5 mm Hg. In summary, the synthetic does not appear to be markedly different to the entire treatment group in diminishing PCWP and kinetics. The confidence limits, however, are large. It is not possible to assert that no differences between the preparations exist.

I think it is reasonable to discount the anomalous animal data (both the kinetics and dynamics). Even if there are differences between the synthetic and recombinant preparations are real, the recombinant preparation should still be approved. The synthetic-peptide preparation would support the proof of concept, that the Natrecor, when produced by either method improves hemodynamics. Dosing recommendations

Figure Global –2 (The error bars are SEM)

Figure 41 (Sponsor's Figure 11)



would be supported only by the results of study #704.325, in particular the effect on those who were treated with the to-be marketed preparation. Again, the results with the synthetically produced preparation, even if slightly different from the recombinant preparation, would be supportive of the dose range proposed for the to-be-marketed recombinant preparation. Since I am only recommending the low dose infusion rate of Natrecor should be approved, I think the safety margin is adequately preserved even if the two formulations are slightly different.

I've not dealt with quality control issues. If the controls define the preparations are equivalent but animals are able to differentiate the two preparations, I'm left with how these two disparate conclusions can be reconciled. One, not unreasonable possibility is that the chemical entities are the same (as demonstrated by adequate chemical characterization) and the differences in the kinetic and dynamic studies are due to the pattern of impurities which differ in the two preparations. An alternate possibility is that these contaminants alter the folding characteristics of the peptide, sufficient to partially modify Natrecor's activity. If that is the case, lot to lot variability is unlikely to yield grossly divergent preparations. I see no choice but to accept, as reasonable, the manufacturing controls as proposed. Once the method of peptide preparation is established, the biological behavior of the preparation should be relatively consistent from lot to lot.

Pharmacology:

The studies reviewed in Dr. Papoian's review are consistent with the published summary of the effects of natriuretic peptides. Since hBNP is of human origin and preferentially reacts with a human receptor, any of the effects of human hBNP with receptors of animal origin, particularly with respect to interpreting dose or concentration effects, should be accepted cautiously.

hBNP increases cGMP in several different biological systems. hBNP induces increases in cGMP from cultured bovine epithelial or cultured aortic smooth muscle cells (Report No. 93-017-70400). When conscious rabbits are given bolus injections of hBNP, plasma cGMP increases. The time course of decay of the cGMP was estimated to be approximately 20.6 ± 5.9 minutes, and approximates the terminal half-life of decay of hBNP in rabbits (see Dr. Papoian's Table 3; p.28 of his review). When rabbits received one or more intravenous boluses (3 ug/kg) of hBNP, urine cGMP increases. Continuous infusion of hBNP at doses of either 0.03 to 0.09 ug/kg/min produce increases in cGMP concentrations in venous blood in conscious dogs, when these dogs were either unpaced or paced (study No 00286).

hBNP, relaxes both arteries and veins. It relaxes phenylephrine- or endothelin- contracted human internal mammary artery and human saphenous veins strips. Dilation of the preconstricted mammary arteries was achieved with nM concentrations of hBNP of (1.8 or 19 nM, when the contracting stimulus was either endothelin or phenylephrine, respectively). Saphenous vein dilation occurred, but even at the highest concentrations, at 1000 nM, less than 50% of the phenylephrine or endothelin –induced constriction was reversed. Assuming the internal mammary artery and saphenous veins are representative of arteries and veins, it would seem that hBNP preferentially dilates arteries rather than veins.

When hBNP is administered either as an intravenous bolus, continuous infusion or subcutaneous bolus hBNP decreases blood pressure in rabbits (Study no. 00159, No 00123).

With respect to cardiovascular function, there are several studies that suggest that hBNP, at most [redacted] has a minimal effect on the electrical and inotropic properties of the heart. Nesiritide infusion, at doses of either 0.03 or 0.09 ug/kg/min infusion, into instrumented conscious dogs (n=6), did not alter the surface ECG characteristics, nor did hBNP alter sinus cycle length, corrected sinus recovery time or A-V conduction (Study No 00286). These doses are within the biologically active range, since plasma cGMP levels were increased and MAP decreased during the infusion.

hBNP does not appear to alter the contractility status in isolated Langendorff-perfused rabbit heart preparations (Study No 00280). hBNP did not increase tension from ventricular trabeculae harvested from explanted failing human hearts and its effect in this study was different from the positive controls, isoproterenol and dobutamine (Study no. 00282).

hBNP may have positive effects on coronary artery blood flow. In paced female swine, hBNP increases coronary artery blood flow, coronary artery cross sectional area and average peak velocity.

With respect to the renal effects, hBNP administered either as multiple bolus (3 ug/kg) to rabbits; increased in urine output as well as urine sodium after each of the doses. There did not appear to be any evidence of habituation or tolerance of these renal effects after each of the three bolus doses.

In summary, hBNP appears to increase cGMP, dilate arteries> veins and cause diuresis (at least in normal rabbits). hBNP does not appear to alter either the electrical or inotropic function of various cardiac model preparations.

Overall Clinical Studies

Dr. Throckmorton's review contains an excellent analysis of Natrecor's clinical development program. Please consult his review with regards to additional details of the pivotal studies. There are three studies (#704.311, #704.325 and #704.326) which are most pivotal to defining the hemodynamic effects of an intravenous bolus followed by constant infusions of Natrecor in patients with various degrees of CHF.

Several other studies were reviewed in my review of the non-pivotal studies. There were a total of six such studies. Five of these studies were in patients with CHF NYHA Class II-IV; the sixth study was in post-operative CABG-surgery patients. In three of the CHF studies, Natrecor was administered as either a bolus or multiple boluses (study #704.305, 704.309, 704.310 and 704.312). Study #704.307 was a placebo controlled, short duration crossover study in patients with CHF who were treated with incremental infusions of Natrecor or placebo. Study #704.306 was a dose-finding, constant-infusion study. None of results of these non-pivotal studies are discordant with the hemodynamic results of the pivotal studies. Several of these non-pivotal studies, are however, useful in defining the kinetics and possibly the dynamic effect of Natrecor.

Pivotal Studies

Table Global-2 briefly summarizes the pivotal studies. The characteristics of the non-pivotal studies are summarized in Table Intr-1 of my review and are not reproduced here. The three pivotal studies differed in the severity of CHF among those enrolled, the duration for which usual therapy was withheld, the duration of blinding during the study, and the requirement of hemodynamic monitoring.

Although this database is relatively modest, adequate information, could be stitched together allow for a description of the effects of Natrecor.

Table Global- 2 Description of Pivotal Studies

	Study #704.311	Study #704.325	Study #704.326
Number Enrolled	Total 103: Placebo = 29 Natrecor 0.25/0.015 ug/kg/min=22 Natrecor 0.5/0.030 ug/kg/min= 26 Natrecor 1.0/0.060 ug/kg/min=26	Total 127 Placebo/standard treatment=42 Natrecor 0.3/0.015ug/kg/min =43 Natrecor 0.6/0.030 ug/kg/min=42	Total =305 Standard treatment=102 Natrecor 0.3/0.015 ug/kg/min=103 Natrecor 0.6/0.030 ug/kg/min=100
Population	CHF requiring hospitalization but not so severe that medications could not be withheld 48 hours	CHF requiring hospitalization yet these subjects could have their medications Withheld for up to 4 hours.	Symptomatic decompensated CHF patients for whom inpatient parentral vasoactive therapy (other than only diuretics) is required.
Blinding	Planned for 24 hours	Planned for the initial 6-hours. Open Label There after	Blinded for doses of Natrecor. Unblinded for standard therapy
Doses: *(B) Bolus (I) Infusions	Placebo: (B) and (I)* Natrecor: 1. (B) 0.25 ug/kg (I) 0.015 ug/kg/min 2. (B) 0.5 ug/kg (I) 0.030 ug/kg/min 3. (B) 1.0 ug/kg (I) 0.06 ug/kg/min	Placebo (B) and (I) Natrecor: 1.(B) 0.3 ug/kg (I) 0.015 ug/kg/min 2.(B) 0.6 ug/kg (I) 0.03 ug/kg/min	Standard therapy or Natrecor: 1.(B) 0.3 ug/kg (I) 0.015 ug/kg/min 2.(B) 0.6 ug/kg (I) 0.03 ug/kg/min
Primary End Point	1. Absolute change in PCWP 2. relative to baseline to 3-hours 3. Absolute change in PCWP 4. relative to baseline to 24-hours	Percentage change in PCWP from pre-treatment while blinded at the 6-hour time point. Using Worst Outcome Analysis	Facilitate clinical assessment of safety Adverse events Laboratory data and Mortality during the first 21 days.
Secondary End-Points	Other hemodynamic endpoints: CI, SVR, MRAP, HR at 3 hours And at 24 hours?	Other hemodynamic measurements CI, SVR, MRAP,HR at 6 hours Using Worst Outcome Analysis	Clinical outcome: Global assessments at 6 and 24 Hours
Titration – Upward?	No procedure for up-titration	No procedure for up-titration	Up-titration for Natrecor at half the initial randomization dose with two possible such up-titrations. at no More frequent than 3 hours.
Swan-Ganz	All	All	To be left to the discretion of the investigator.

Studies #704.311 and #704.325 contain placebo-controlled results that define the hemodynamic effects of Natrecor. Durability and stability of Natrecor's effect was established by the placebo-controlled 24-hour data of study #704.311 and to a lesser extent the uncontrolled data from study #704.325. The placebo-controlled offset data from study #704.311 also confirms duration of Natrecor's effect. The onset of hemodynamic effects was derived from the early time course of Natrecor wedge pressure drops during studies #704.311 and #704.325.

Placebo-controlled symptom benefit was captured by the results of the six-hour time point of study #704.325, and to a lesser extent from the open-labeled benefit in study #704.326. Any effect on net fluid output and patient weights was derived from the data on fluid intake and urine output from studies #704.311 and #704.325 and weights from study #704.325 and #704.326. Lastly, mortality, duration of hospital stay and re-hospitalization rates is summarized from the effects across all three studies.

All three studies contain at least some dose response information; study #704.311 contains the largest span of doses and also includes a placebo group. Both studies #704.325 and #704.326 contain two dose of Natrecor. The first six hours of study #704.325 was placebo-controlled and positive controlled thereafter. Study #704.326 was positive-controlled.

Demographics: I've tabulated selected demographics across the three pivotal studies (Table Global-3). Signs/symptoms of CHF were fairly constant across all three studies. The frequency of such symptoms such as rales and edema did not seem that much greater in the patients with greater severity of CHF.

Table Global- 3 Selected Demographics and Symptoms of the Pivotal Studies.

Parameter	Study 704.311				Study 704.325			Study 704.326		
	Placebo	Nesiritide							Nesiritide	
		0.25/0.015	0.5/0.030	1.0/0.060					0.015	0.03
Age (yrs) mean ± SD	53.7 ± 8.0	56.7 ±12	56.7 ±13	58.2 ±12				63 ± 14	63 ± 14	65 ±12
Weight (kg) mean ± SD	77.4 ±10	89.8 ±25	79.8 ±21	80 ±21				80 ± 21	83 ± 24	79 ± 19
Race: # (%)										
White	10 (34)	15 (68)	14(54)	17(65)				69 (68)	61 (59)	71 (71)
Black	9 (31)	6 (27)	6(23)	5(19)				19 (19)	28 (27)	20 (20)
Asian	0	0	1(4)	1(4)				2 (2)	1 (1)	0
Hispan	(24)	1(5)	5(19)	3(12)				12 (12)	11 (11)	8 (8)
Other	3 (10)	0	0	0				0	2 (2)	1 (1)
Male # (%)	21 (72)	18 (82)	21 (81)	23 (88)				73 (72)	67 (65)	67 (67)
NYHA										
I	0	0	0	0				0	0	1 (1)
II	0	2 (9)	2 (8)	2 (8)				6 (6)	6 (6)	11 (11)
III	21 (72%)	14 (64)	13 (50)	15 (58)				61 (60)	57 (55)	52 (52)
IV	8 (28%)	6 (27)	11 (42)	9 (35)				35 (34)	40 (39)	36 (36)
EF	18.5 ± 7	22.4 ± 7	19.4 ± 7	24.2 ± 7						
Signs/Symptoms # (%)										
Rales	11 (41)	11 (58)	12 (46)	13 (62)	30 (71)	22 (51)	24 (57)	66 (65)	68 (66)	69 (69)
Edema	11 (42)	11 (58)	12 (46)	13 (36)	31 (74)	27(63)	24 (57)	73 (72)	76 (71)	71 (71)
S3	20 (74)	12 (63)	20 (77)	11 (50)	36 (86)	36 (84)	31 (74)	51 (50)	51 (50)	56 (56)
S4	23 (85)	17 (89)	22 (85)	19 (86)	10 (24)	7 (16)	9 (21)	25 (25)	22 (21)	22 (22)

Those enrolled did not include subjects whose decompensated heart failure resulted from an acute insult such as a myocardial infarction, but consisted of a population with an acute exacerbation of ongoing, stable CHF.

Patient Dispositions- Table Global-4 lists the evaluability status of those who entered into the clinical studies. In several studies, patients who required additional therapy were imputed as a "worst outcomes"

value. According to the sponsor, even those who discontinued but received some inotropic support were also considered in the "worse outcome" category.

Table Global- 4: Patients Disposition Pivotal Studies.

	Study 704.311				Study 704.325			704.326		
	Placebo	Nesiritide			Placebo	Nesiritide		Standard Treatment	Nesiritide	
		0.25/ 0.015	0.5/ 0.030	1.0/ 0.060		0.3/ 0.015	0.6/ 0.030		0.3/ 0.015	0.6/ 0.030
# Enrolled	29	22	26	26	42	42	42	102	103	100
# Completed on Random. Dose and had Evaluable 3 or 6 Hour Measurements (PCWP) or Symptom assessment*	29	16	17	19	35	36	38	100	101	94

* Please refer to footnote 1 for caveats of each study.

Primary End-Points: Acute hemodynamic responses: PCWP (at 3 or 6 hours)

Study 704.311: Although labeled as an 'intent-to-treat" analysis, there were subjects whose hemodynamic measurements were never measured and no value was imputed. The intent-to treat nomenclature, according to the sponsor, refers to those subjects who received a dose other than the randomized dose. These subjects were included within the analyses of the randomized group. Those subjects who discontinued were, however, not included in any group for analysis. This analysis is, therefore, mislabeled and is really a "per-dose" analysis.

The number of subjects who were discontinued and/or had no values available for PCWP at either the 3 and 24 hour time point are tabulated below (see table Global-5).

Table Global- 5. # Of Subjects Excluded From the Intent-to-Treat Analyses Study #704.311 (Table 4 sponsor V 55 p 147).

	Placebo	0.015 ug/kg/min	0.03 ug/kg/min	0.06 ug/kg/min
3 hours	0	1	3	2
24 hours	4	1	5	7

Table Global-6 contains the sponsor's analysis of change of PCWP at 3 hours. Dr. Cui's, reanalyzed the data by including a baseline covariate term. The database for analysis excludes those who discontinued and is therefore, also not an intent-to-treat analysis. Table 6.1.12.5.3. of Dr. Throckmorton's review (not reproduced here) contains an analysis, with the last observation carried forward, for the 3 hour time point. The conclusions of Dr. Cui's, the last value carried forth and the sponsor's analyses are virtually the same.

Table Global-6: Study 704.311 the sponsor's "ITT" analysis[5]

		Sponsors "ITT" mean ± SD	p-value*		Dr. Cui's Model	
3 hours	Placebo	-1.8 ± 4.6	overall		-2.3	overall
	Nesiritide 025/0.015 ug/kg/min	-8.9 ± 8.7	p- value		-7.7	p-value #
	Neseritide 0.5/0.03 ug/kg/min	-6.0 ± 7.9	0.002*		-7.5	0.0001
	Neseritide 1.0/0.06 ug/kg/min	-10.7 ± 8.3			-10.2	

*Compared to Placebo Omnibus p-value. Not corrected for two primary endpoints.
#-Not corrected for multiple endpoints, those who did not have measurements at 3-hours were censored

Study 704.325: The primary end-point was the percentage change from baseline in PCWP at the 6-hour time point. Any subject who required intervention or who was unblinded as to therapy prior to 6 hours of infusion was assigned a "worst outcome" classification. Patients who discontinued

[5] The sponsor has apparently included several additional analysis will be included in the briefing document. These analyses include truncating those who enrolled to the cohort consisting of at the 20/group . The results are nearly equivalent.

because of adverse events and required some form of inotropic support were also classified as "worst outcomes". The effect at 6 hours is shown in Global-7. Nominal p-values were derived from a non-parametric analysis. Table Global-7 also includes the effect of the cohort of subjects who received the synthetic preparation of Natrecor. No subjects who received the synthetic preparation were classified as "worst outcomes' so the mean value for this cohort was calculated.

Table Global-7 Study 704.325 Primary 6-Hour "Worst Outcome" Analysis for PCWP

Treatment	Median % Change form baseline	p-value
Placebo	+7.3	<0.001
Nesiritide 0.3/0.015 ug/kg/min	-20.0	
Nesiritide 0.6/0.03 ug/kg/min	-32.6	
Nesiritide 0.3/0.015 ug/kg/min Synthetic preparation (n=8) Mean ± SEM	-14.8 ±8.8	
Nesiritide 0.6/0.03 ug/kg/min Synthetic preparation (n=8) Mean ± SEM	-30.6 ± 5.1	

Given the highly significant p-values, it appears that Nesiritide at either 3 (study #704.311) or 6 hour time point (Study #704.325) decreases PCWP in CHF patients, relative to placebo.

PCWP after 24-hours of infusion:

The persistence of Natrecor's effect on PCWP after 24-hours of infusion is supported by the data from study # 704.311. This data is shown in Table Global-8. Patients who had no evaluable PCWP values were censored (despite the sponsor's nomenclature defining this study as an ITT). Table 6.1.12.5.3. of Dr. Throckmorton's review (not reproduced here) contains an analysis, with the last observation carried forward, for the 24 hour time points. The results do not significantly differ from the results shown in Table Global- 8.

Table Global-8. Study 704.311 Effect at 24 hours on PCWP The sponsor-defined "ITT" group (really a per randomized group).

Time	Number (Number Missing)	Treatment	Sponsors "ITT" mean ± SD	p-value*		Dr. Guil Mean	
24 hours	25 (4)	Placebo	-1.8 ± 6			[redacted]	[redacted]
	21 (1)	Nesiritie 025/0.015 ug/kg/min	-8.3 ± 7	overall p-value		[redacted]	[redacted]
	21 (5)	Nesiritide 0.5/0.03 ug/kg/min	-3.7 ± 6			[redacted]	
	19 (7)	Nesiritide 1.0/0.06 ug/kg/min	-8.4 ± 6.41	0.001#		[redacted]	

Includes Term for Baseline Measurements. Missing values were censored.

Other Hemodynamic Parameters: The effects of Natrecor on the other hemodynamic parameters for study #704.311 (derived from sponsor's Tables 20b, 21b, 23b and 33b vol 54 pp. 150-280) are shown in Table Global-9. The p-values are nominal and not corrected for multiple primary end points (at 3 and 24 hours) nor are they corrected for multiple parameters (CI, MRAP, SVR and HR). As noted above, these are not true ITT analyses.

At 3-hours, there is an apparent effect on MRAP (decrease), SVR (decrease) and CI (increase). At 24-hour, however, Natrecor does not appear to significantly alter the other hemodynamic parameters relative to placebo. At 24 hour, MRAP and SVR were still in the same direction as after three hours, but with a diminished and non-significant magnitude. It is unclear if Natrecor has an effect on CI at 24 hours. The nominal p-value probably reflects a comparison with the mid-dose and high dose Natrecor groups. Numerically for CI, placebo at 24-hours was superior to the mid-dose Natrecor group.

Table Global- 9 Other Hemodynamic Effects at 3 and 24 hours 'ITT" groups Study #704.311. Change from Baseline

Parameter	Placebo	Neseritide 0.25/0.015ug/kg/min	Nesiritide 0.5/0.030ug/kg/min	Nesiritide 1.0/0.060 ug/kg/min	Nominal p-value*
3 Hour Effects					
MRAP (mm Hg)	-0.8 ± 3.7	-3.7 ± 3.5	-3.3 ± 4.3	-4.5 ± 6.2	0.024
SVR (Dynes.sec cm-^{5})	-16.4 ± 397	-364 ± 863	-203 ± 492	-500 ± 426	0.017
CI (L/min/M+)	0 ± 0.4	0.4±0.6	0.3 ± 0.5	0.7 ± 0.7	0.000
HR (BPM)	2.6 ± 7.6	-3.7 ± 6.7	-2.2 ± 8.9	6.2 ± 13.9	0.002

24 hour Effect					
MRAP (mm Hg)	-1.4 ± 5.2	-2.6 ± 3.9	-3.6 ± 6.0	-2.9 ± 3.7	0.493
SVR (Dynes.sec cm-^{5})	17.6.± 676	-283 ± 680	-67 ± 776	-354 ± 301	0.266
CI (L/min/M+)	0.1 ± 0.3	0.2±0.5	0.0 ± 0.7	0.4 ± 0.4	0.032
HR (BPM)	4.5 ± 11.2	-1.0 ± 6.8	-0.2 ± 7.6	4.0 ± 8.2	0.083

* Sponsor's analysis , uncorrected for multiple end-points time 3 and 24 hours and number of parameters)

With respect to study #704.325, only the 6-hour data for placebo-controlled hemodynamic parameters was available (Table Global 10). After 6 hours, standard treatment was made available to placebo patients.

Table Global-10 Median Values (25-75 percentiles) for Hemodynamic Parameters Last Observation Carried Forward Analysis Study 704.325 (6 Hour Time Point). Data derived from Sponsor's Tables 27B, 28B, 30B and 40B:

	placebo	0.3/0.015 ug/kg/min	0.6/0.030 ug/kg/min	p-value
MRAP (mm Hg)	0 (-2.0 to 3.0)	-2.5 (-5.5 to -1.0)	-2.5 (-5.0 to 0)	0.001
SVR (Dynes.sec cm-^{5})	124.2 (-151 to 308)	-147 (-393 to 37)	-342 (-517 to -135)	0.000
CI (L/min/M+)	0 (-0.6 to 0.2)	0.2 (-0.1 to 0.4)	0.4 (0 to 0.0)	0.000
HR (BPM)	0.5 (-2.0 to 5.0)	-3.0 (-6.0 to 1.0)	0 (-4.0 to 4.0)	0.218

In summary, PCWP appears to be altered by all doses of Natrecor at both 3, 6 and 24 hours. The effect of Natrecor on the other hemodynamic parameters (CI, SVR and MRAP) appears to be compatible with improved hemodynamics at 3 and 6 hours but not convincingly at 24 hours.

Symptomatic Benefit: The sponsor collected placebo-controlled symptom relief data during the first 6-hours of Study #704.325. The sponsor collected similar data, but positive-controlled, from study #704.326.

The components of the symptom assessments were a global assessment both by the physician, and the patient and a six point patient questionnaire[6]. All three assessments were administered at baseline, 6 hours and 24 hours during Study #704.325 and #704.326.

Any interpretation of the QOL for study #704.325 must be tempered by the potential bias engendered in the study design (see p. 5 of this review), by the limited degree of treatment blinding (only for 6 hours) and by the lack of validation of the sign/symptom questionnaire.

Despite the lack of complete confidence in blinding, some credibility can be given to the results of the various symptoms and quality of life assessments. There were a large number of investigators (> 45). It is quite clear that no single investigator enrolled a sufficient number of patients to bias the conclusion with respect to symptom benefit. Subtler forms of a more general bias cannot, however, be excluded.

Table Global-11 contains both baseline measurements as well as change in the six point symptom assessment from study #704.325. Table Global- 12 contains the physicians overall and Table Global-13 the patient's overall assessment from this study. Tables 14,15 and 16 contain the corresponding data for study #704.326

[6] The following questions and categories formed the basis of the questionnaire:

1. Breathing Difficult: a)None b)With Moderate Activity c)With Minimal Activity d) At Rest
2. Appetite: a)Good b)Decreased c)No appetite
3. Peripheral Circulation: a) Extremities Well Perfused and Warm b) Extremities Cool with Decreased Perfusion c) Extremities Cold and Vasoconstricted
4. Fatigue: a) No fatigue b) Fatigue with Moderate Activity c) Fatigue with Minimal Activity d) Fatigue at Rest
5. Lightheadedness : a)No Lightheadedness b) Lightheadedness with Moderate Activity c) Lightheadedness with Minimal Activity d) Lightheadedness at Rest
6. Peripheral Edema: a) None b) Mild c) Moderate d) Severe

Baseline characterization of the symptoms was followed at 6 and 24 hours by assessing whether the symptoms were either: i) Improved ii) No change or iii) Worse than baseline.

Table Global-11 Study 704.325: Symptoms Six Point Scale.

	Study 704.325 6-Hour Time Point				Study 704.325 24-hour Time Point			
	PBO (n=42)	Nesiritide 0.3/0.015 (n=43)	Nesiritide 0.6/0.030 (n=42)	p-value	PBO (n=42)	Nesiritide 0.3/0.015 (n=43)	Nesiritide 0.6/0.030 (n=42)	p-value
Breathing Difficulty Baseline:								
No difficulty	3 (7%)	2 (5%)	4 (10%)	0.628				
With Moderate Activity	7 (17%)	5 (12%)	4 (10%)					
With Minimal Activity	22 (52%)	23 (53%)	21 (50%)					
At Rest	10 (24%)	13 (30%)	13 (31%)					
Change:								
Improved	5 (12%)	22 (56%)	20 (50%)		25 (66%)	29 (73%)	33 (79%)	
No Change	27 (64%)	16 (41%)	18 (45%)	<0.001	12 (32%)	9 (23%)	7 (17%)	0.513
Worse Than Baseline	10 (24%)	1 (3%)	2 (5%)		1 (3%)	2 (5%)	2 (5%0	
Appetite Baseline								
Good Appetite	22 (52%)	20 (47%)	2 (57%)	0.63				
Decreased Appetite	14 (33%)	19 (44%)	15 (36%)					
No Appetite	6 (14%)	4 (9%)	3 (7%)					
Change:								
Improved	3 (7%)	11 (28%)	2 (8%)		10 (26%)	10 (25%)	14 (33%)	
No Change	38 (90%)	27 (69%)	35 (88%)	0.017	27 (71%)	29 (73%)	26 962%)	0.804
Worse Than Baseline	1 (2%)	1 (3%)	2 (5%)		1 (3%)	1 (3%)	2 (5%)	
Peripheral Circul Baseline:								
Extr. Warm & well perfus.	26 (62%)	18 (42%)	26 (62%)	0.106				
Extr Cool with Decr perfus	12 (29%)	21 (49%)	15 (36%)					
Extr Cold & Vasoconst.	4 (10%)	4 (9%)	1 (2%)					
Change:								
Improved	2 (5%)	7 (18%)	6 (15%)		9 (24%)	11 (28%)	10 (245)	0.849
No Change	40 (95%)	31 (79%)	34 (85%)	0.274	27 (76%)	29 (73%)	31 (74%)	
Worse Than Baseline	0 (0%)	1 (3%)	0 (0%)		0 (0%)	0 (0%)	1 (2%)	
Fatigue Baseline:								
No fatigue	2 (5%)	1 (2%)	2 (5%)					
With Moderate Activity	9 (21%)	7 (16%)	4 (10%)	0.2533				
With Minimal Activity	21 (50%)	22 (51%)	20 (48%)					
At Rest	10 (24%)	13 (30%)	16 (38%)					
Change:								
Improved	2 (5%)	12 (32%)	15 (38%)		12 (32%)	17 943%)	25 (60%)	0.062
No Change	35 (83%)	25 (66%)	24 (60%)	<0.001	24 (63%)	21 (53%)	15 (36%)	
Worse Than Baseline	4 (12%)	1 (3%)	1 (3%)		2 (5%)	2 (5%)	2 (5%)	
Lightheadedness Baseline:								
None	32 (76%)	29 (67%)	32 (76%)					
With Moderate Activity	4 (10%)	5(12%)	2 (5%)	0.592				
With Minimal Activity	5 (12%)	5 (12%)	3 (7%)					
At Rest	1 (2%)	4 (9%)	5 (12%)					
Change:								
Improved	2 (5%)	9 (24%)	4 (10%)		3 (8%)	8 (20%)	6 (14%)	
No Change	39 (93%)	29 (76%)	34 (85%)	0.023	34(89%)	32 (80%)	36 (86%)	0.211
Worse Than Baseline	1 (2%)	0 (0%)	2 (5%)		1 (3%)	0 (0%)	0 (0%)	
Periph'l Edema Baseline:								
None	13 (31%)	13 (30%)	19 (45%)					
Mild	19 (45%)	15 (35%)	13 (31%)	0.382				
Moderate	6 (14%)	12 (28%)	6 (14%)					
Severe	4 (10%)	3 (7%)	4 (1050					
Change:								
Improved	3 (7%)	8 (21%)	9 (23%)		21 (55%)	18 (45%)	21 (50%)	0.612
No Change	36 (86%)	30 (79%)	31 (78%)	0.028	17 (45%)	21 (53%)	20 (48%)	
Worse Than Baseline	3 (7%)	0 (0%)	0 (0%)		0 (0%)	1 (3%)	1 (2%)	

Overall Assessments: At 6-hours, there is clear benefit to symptoms as judged by either patient or physician. At 24 hours, no differences remained. The convergence of symptom benefit is not surprising since concurrent standard therapies were allowed after 6 hours.

Table Global-12 Patient's Global Assessment at 6 and 24 Hours study #704.325

	Study 704.325 6 Hours				Study 704.325 24 Hours			
	Placebo	Nesiritide		p-Value		Nesiritide		p-Value
		0.3/0.015	0.6/0.030		Placebo	0.3/0.015	0.6/0.030	
Markedly Better	0 (0%)	5 (13%)	3 (8%)	0.000	6 (16%)	9 (23%)	10 (24%)	0.337
Better	6 (14%)	19 (48%)	23 (59%)		22 (58%)	23 (58%)	26 (63%)	
No Change	31 (74%)	10 (25%)	9 (23%)		9 (24%)	5 (13%)	3 (7%)	
Worse	2 (5%)	2 (5%)	2 (5%0		1 (3%)	3 (8%)	2 (5%)	
Markedly Worse	3 (7%)	4 (10%)	2 (5%)		0 (0%)	0 (0%)	0 (0%)	

Table Global- 13 Physician Global Assessments at 6 and 24 hours study #704.325:

	Study 704.325 6 Hours				Study 704.325 24 Hours			
	Placebo	Nesiritide		Nominal p-Value		Nesiritide		Nominal p-Value
		0.3/0.015	0.6/0.030		Placebo	0.3/0.015	0.6/0.030	
Markedly Better	0 (0%)	5 (13%)	4 (10%0	0.000	5 (13%)	7 (18%)	9 (21%)	0.440
Better	2 (5%)	17 (43%)	26 (67%)		23 (61%)	25 (63%)	27 (64%)	
No Change	28 (67%)	10 (25%)	6 (15%)		9 (24%)	[illegible]	[illegible]	
Worse	9 (22%)	4(10%)	1 (15%)		1 (3%)	[illegible]	[illegible]	
Markedly Worse	3 (7%)	4 (10%)	2 (5%)		0 (0%)	[illegible]	[illegible]	

Study #704.326:

Patient's six point questionnaire data is shown in Table Global- 14. There did not appear to be any benefit in Natrecor, relative to standard therapy, at either 6 or 24 hours. There did not appear to be a benefit in the higher dose of Natrecor when compared to the lower Natrecor dose. There was attrition in the number of patients had valid assessments at 6 and 24 hours. The reason for attrition is largely due to those whose measurements were outside the pre-specified (5.5-7.0 hours for the six-hour time point and 20-28 hour interval for the 24-hour time point) intervals.

Global Assessments: Patient's and Physician's overall assessments are shown in Tables Global-15 and Global-16, respectively. There was no symptomatic benefit of Natrecor infusions relative to standard care nor were symptoms improved in a dose-related manner.

Table Global-14 Study 704.326: Symptoms Six Point Rating Scale

	Study 704.326 6-Hour Time Point				Study 704.326 24-hour Time Point			
	Standard Care (n=102)	Nesiritide 0.3/0.015 (n=103)	Nesiritide 0.6/0.030 (n=100)	p-value)	Standard Care (n=102)	Nesiritide 0.3/0.015 (n=103)	Nesiritide 0.6/0.030 (n=100)	p-value
Breathing Difficulty Baseline:								
No difficulty	0 (0%)	2 (2%)	2 (2%)	0.597				
With Moderate Activity	13 (13%)	19 (19%)	19 (19%)					
With Minimal Activity	59 (58%)	53 (52%)	46 (47%)					
At Rest	29 (29%)	27 (27%)	31 (32%)					
Change:								
Improved	52 (61%)	56 (63%)	44 (55%)		77 (80%)	77 (78%)	63 (70%)	
No Change	30 (35%)	32 (36%)	35 (44%)	0.583	14 (15%0	18 (18%)	20 (22%)	0.23
Worse Than Baseline	3 (4%)	1 (1%)	1 (1%)		5 (5%)	4 (4%)	7 (8%)	
Appetite Baseline								
Good Appetite	42 (42%)	37 (37%)	47 (48%)	0.351				
Decreased Appetite	43 (43%)	52 (51%)	40 (41%)					
no Appetite	16 (16%)	12 (12%)	11 (11%)					
Change:								
Improved	19 (23%)	24 (62%)	16 (20%)		40 (42%)	39 (39%)	28 (31%)	
No Change	62 (74%)	62 (70%)	59 (75%)	0.534	50 (2%)	57 (58%)	54 (61%)	0.263
Worse Than Baseline	3 (4%)	3 (3%)	4 (5%)		6 (6%)	3 (3%)	7 (8%)	
Peripheral Circle Baseline:								
Extr. Warm & well perfus.	39(39%)	51 (50%)	48 (49%)	0.132				
Extr Cool with Decr perfus	50 (50%)	42 (42%)	44 (45%)					
Extr Cold & Vasoconst.	12 (12%)	8 (8%)	6 (6%)					
Change:								
Improved	23 (27%)	25 (28%)	21 (27%)		29 (30%0	38 (38%)	29 (33%)	0.300
No Change	60 (71%)	64 (72%)	57 (72%)	0.910	65 68%)	61 (62%)	55 (62%)	
Worse Than Baseline	2 (4%)	0 (0%)	1 (1%)		2 (2%)	0 (0%)	5 (6%)	
Fatigue Baseline:								
No fatigue	2 (2%)	6 (6%)	0 (0%)					
With Moderate Activity	16 (16%)	21 (21%0	21 (21%)	0.05				
With Minimal Activity	42 (42%)	38 (38%)	58 (59%)					
At Rest	41 (41%)	35 (35%)	19 (19%)					
Change:								
Improved	25 (30%)	26 (30%)	26 (33%)		53 (55%)	54 (455)	46 (51%)	0.807
No Change	52 (62%)	59 (67%)	49 (62%)	0.787	36 (38%)	38 (39%)	37 (41%)	
Worse Than Baseline	7 (8%)	3 (3%)	4 (5%)		7 (7%)	6 (6%)	7 (8%)	
Lightheadedness Baseline:								
None	57 (56%)	56 (56%)	58 (59%)					
With Moderate Activity	12 (12%)	20(20%)	15 (15%)	0.868				
With Minimal Activity	25 (25%)	17 (17%)	7 (17%)					
At Rest	7 (7%)	7 (7%)	8 (8%)					
Change:								
Improved	11 (13%)	17 (19%)	11(14%)		25 (26%)	26 (27%)	18 (20%)	
No Change	72 (86%)	67 (76%)	61 (77%)	0.369	67(70%)	66 (67%)	68 (76%)	0.0.742
Worse Than Baseline	1 (1%)	4 (5%)	7 (9%)		4 (4%)	6 (6%)	3 (3%)	
Periph'l Edema Baseline:								
None	29 (29%)	28 (28%)	29 (30%)					
Mild	33(33%)	23 (23%)	27 (23%)	0.382				
moderate	32 (32%)	33 (33%)	30 (31%)					
Severe	7 (7%)	17 (17%)	12 (12%)					
Change:								
Improved	16 (19%)	30 (34%)	25 (31%)		49 (51%)	56 (57%)	43 (48%)	0.467
No Change	68 (80%)	59 (66%)	54 (68%)	0.060	46 (48%)	43 (43%)	47 (52%)	
Worse Than Baseline	7 (7%)	0 (0%)	1(1%)		1 (1%)	0 (3%)	0 (0%)	

Based on the results of study #704.325, and excluding concerns of blinding and cross-contamination of the symptom assessment with the hemodynamic measurements, relative to placebo, Natrecor appears to improve symptoms in patients with CHF. Based on the results of study #704.326, there

was no symptom benefit in comparing Natrecor to standard treatments. The two doses of Natrecor appear to be equivalent.

Table Global-15 Patient's Overall Assessment at 6 and 24 Hours Study #704.326

	Study 704.326 6 Hours				Study 704.326 24 Hours			
	Standard Care (n=102)	Nesiritide		p-Value	Standard Care (n=102)	Nesiritide		p-Value
		0.3/0.015 (n=103)	0.6/0.030 (n=100)			0.3/0.015 (n=103)	0.6/0.030 (n=100)	
Markedly Better	8 (10%)	10 (12%)	4 (5%)	0.318	17 (18%)	[redacted]	[redacted]	0.302
Better	46 (55%)	48 (%)	45 (55%)		57 (62%)	[redacted]	[redacted]	
No Change	27 (32%)	10 (25%)	29 (35%)		16 (17%)	[redacted]	[redacted]	
Worse	3 (4%)	2 (5%)	4 (5%)		2 (2%)	[redacted]	[redacted]	
Markedly Worse	0 (0%)	4 (10%)	0 (0%)		0 (0%)	[redacted]	[redacted]	
	total n=84	total n=86	total n=82		total n=92	[redacted]	[redacted]	

Table Global- 16 Physician's Overall Assessments at 6 and 24 Hours Study #704.326.

	Study 704.326 6 Hours				Study 704.326 24 Hours			
	Standard Care (n=102)	Nesiritide 0.3/0.015 (n=103)	Nesiritide 0.6/0.030 (n=100)	p-Value	Standard Care (n=102)	Nesiritide 0.3/0.015 (n=103)	Nesiritide 0.6/0.030 (n=100)	p-Value
Markedly Better	2 (2%)	5 (%)	4 (5%)	0.362	15 (16%)	[redacted]	[redacted]	0.263
Better	51 (61%)	55 (64%)	46 (56%)		62 (67%)	[redacted]	[redacted]	
No Change	28 (33%)	25 (29%)	29 (35%)		11 (12%)	[redacted]	[redacted]	
Worse	2 (2%)	1(1%)	3 (4%)		4 (4%)	[redacted]	[redacted]	
Markedly Worse	1 (1%)	0 (0%)	0 (0%)		1 (1%)	[redacted]	[redacted]	
	total n=84	total n=86	total n=82		total n=93	[redacted]	[redacted]	

Study #704.325: Persistence of Initial Therapy: Most subjects allocated to the low dose infusion of Natrecor remained on their initial dose. Only approximately half of those allocated to high dose Natrecor patients remained on the initial dose. The reason for dose modification during the clinical study is shown in Global-17. More patients had doses changed in the high dose group for either symptom improvement or hypotension.

Table Global-17 Reason for Dose Modification Study #704.325

	Neseritide Dose*		p-value
	0.015 ug/kg/min	0.030ug/kg/min	
Number Enrolled	43	42	
Number With Dose Modified	6	19	0.002
Modification			
Dose Increased (Followed Reduction or Interruption)	1	6	0.058
Dose Reduction	5	17	0.003
Dose Interruption	1	5	0.110
Reason for Reduction and or Interruption			
Clinical Improvement	2	9	0.026
Hypotension	3	7	0.195
Worsening CHF	1	0	1.00
Other Adverse Event	1	1	1.00
per Protocol	0	0	-----
Hospital/Administrative Policy	0	0	-----
Inadequate Therapeutic Response	0	0	-----
Other	1	3	0.36

* A bolus was administered prior to the constant infusion

Study #704.326: Persistence on Initial Therapy: Subjects were more frequently left on the initial drug when they were allocated to standard therapy in study #704.326 See Table Global 18). Not surprising, more subjects in the standard therapy required upward and downward titration to optimize hemodynamic effects. The reason for change in dose was more frequently "improvement in symptoms" in the standard care group. More subjects in the high dose than low dose Natrecor group had their dose modified. Most of these subjects had their dose modified due to hypotension.

Table Global-18 Modification of Doses in Study #704.326

	Standard Treatment	hBNP 0.015 ug/kg/min	h-BPN 0.03 ug/kg/min	p-Value
Number Enrolled	102	103	100	
Number Who Did Not Receive A New Vasoactive Drug	92 (90%)	86 (83%)	76 (76%)	0.027
Number With Initial Drug Discontinued and a New Vasoactive Agent Was Subsequently Initiated	2 (2%)	9 (9%)	12 (12%)	0.013
Number Who Continued On Treatment But Had A Vasoactive Drug Added	8 (8%)	8 (8%)	12 (12%)	0.511
Number of Subjects Remaining on Initial Dosing Regimen	50 (50%)	73 (71%)	57 (57%)	0.007
Number Who Had Dose Modified	51 (50%)	30 (29%)	43 (43%)	0.007
Clinical Improvement	25 (25%)	6 (6%)	6 (6%)	0.000
Physician choice	17 (17%)	7 (7%)	6 (6%)	0.023
Inadequate Clinical Response	14 (14%)	10 (10%)	11 (11%)	0.674
Titration	20 (20%)	3 (3%)	4 (4%)	0.000
Hypotension	4 (4%)	17(17%)	28 (28%)	0.000
Other Adverse Events	13 (13%)	7(7%)	9 (9%)	0.357
Other	12 (12%)	6(6%)	10 (10%)	0.295

Fluid Balances:

Natrecor treatment did not consistently increase net fluid output, despite its ability to decrease wedge pressure and increase in cardiac output. The database for which urine output and fluid intake was recorded consists of two pivotal studies and two non-pivotal studies. The third large pivotal study #704.326 did not measure urine output and fluid intake, but did track weight for eight days. In the non-pivotal studies, Natrecor was administered to CHF patients as multiple boluses.

There were two moderately sized exposures of CHF patients to bolus Natrecor (studies #704.309 and #704.310). Net urine flow in Natrecor treated patients did not appear to be increased. Sodium excretion also did not appear to be increased among these patients (data not shown here).

The effect of Natrecor treatment on urine output for the 24-hour time interval during study 704.311is shown in Table Global-19. The effects of Natrecor treatment during the double-blind portion of study #704.325 (0-6 hours) and the whole 24-hour interval of the study, are also shown in Table Global-19. It is not possible to come to a definitive conclusion about fluid changes while on Natrecor. The results of study #704.311 suggest fluid retention (not statistically significant) with increasing doses of Natrecor. The results of study #704.325 over the first six hours suggests a mild, but statistically significant, increase in urine output and net fluid loss (output-intake), relative to placebo. However, over the whole 24-hour period, during which diuretic use was allowed after hour six, urine output and net fluid statistically favored placebo. The lack of differences between placebo and Natrecor during the whole 24 hour period could be partly attributed to the increased use of diuretics in the placebo group. Sodium excretion during study #704.311 favored placebo during the 24- hour observation period. Fluid and sodium balances were not collected during study #704.326 but daily weight was collected.

Weight:

With respect to overall weight changes, the sponsor did not tabulate the change in patient's weight as a result of therapy during study #704.311. Weights, however, were measured. Weight loss during study #704.325 numerically, but not statistically, favored Natrecor treatment during days 2 and 3 of the five days during which weight was measured, but there was a non-significant difference as of day 5. The order of.

Table Global-19 Fluid Balance and Sodium Excretion Studies #704.311 and #703.325

Study 704.311					
Values are Mean ± SD	Placebo (n=29)	Nesiritide			
		0.25/0.015 (n=22)	0.5/0.030(n=26)	1.0/0.060 9n=26	p-value
Fluid Intake (ml/24 hr)	1935 ± 515	1836 ± 427	1767 ± 545	2147 ± 1062	0.222
Urine Output (ml/24 hour)	2410 ± 1086	1745 ± 840	1479 ± 806	2011 ± 1845	0.041
Output –Intake (ml/24hr)	475 ± 1094	(-91 ± 756)	(-287 ± 848)	(-136 ± 1845)	0.113
Urine Sodium Excretion	156 ± 91	85 ± 58	104 ± 80	146 ± 285	0.369
Study 704.325 0 to 6 Hours					
	Placebo (n=42)	Nesiritide			
		0.3/0.015 (n=43)	0.6/0.030 (n=42)		p-value
Fluid Intake (ml/hr)	96.2 ± 53	98.3 ± 41	94.1 ± 58		0.936
Urine Output (ml/hr)	63.9 ± 43	92 ± 60	110 ± 73		0.01
Output –Intake (ml/hr)	(-32.3 ± 70)	(-3.3 ± 71)	+15.9 ±71		0.039
Study 704.325 0 to 24 hours					
Fluid Intake (ml/hr)	78.6 + 26	82.1 + 24	83 + 25		0.702
Urine Output	136.2 + 56	102.6 + 47	89.9 + 47		<0.001
Output –Intake (ml/hr)	+ 57.8 ± 60	+20.7 ± 47	+6.9 ± 47		<0.001

weight loss was Nesiritide 0.6/0.03 ug/kg/min > PBO-standard treatment > Nesiritide 0.30/.015 ug/kg/min. With respect to study #704.326, weight decreased in the standard therapy group as well as the two Natrecor treatment groups. In summary, there was no strong signal suggesting a different effect weight loss by any or the treatments.

Hospitalizations and Duration of Hospitalization:

Studies #704.325 and #704.326 enrolled subjects who, in the opinion of the investigator, required hospitalization for decompensated CHF (see Table Global-20). During study #704.325, more subjects in the placebo-controlled/standard therapy group were discharged by day 21 (this was a protocol pre-specified follow-up date), and fewer of these subjects were later re-hospitalized (through day 21), than the Natrecor groups. The results of study #704.326 went in the opposite direction. When comparing standard therapy to Natrecor, more of those on standard therapy remained hospitalized through day 21 and of those discharged, more were re-hospitalized. Considering the outcomes from both studies, there does not appear to be an overwhelming or consistent signal that either the duration of hospitalizations or the frequency of re-hospitalizations are either reduced or increased when Natrecor is compared to either placebo/standard treatment or standard CHF treatment. There were five subjects, all Natrecor treated subjects who were hospitalized during study #704.311.

Table Global-20 Discharge/Readmission Data Studies #704.325 and #704.326

	Study #704.325			Study #704.326		
	Placebo-Control	Nesiritide		Standard Treatment	Nesiritide	
		0.3/0.015	0.6/0.030		0.3/0.015	0.6/0.03
# Enrolled	42	43	42	102	103	100
# D/C'd by Day 21	40	35	34	97	101	96
Readmitted by Day 21	1	4	4	16	8	11
# D/C'd by Day 21 and Not Readmitted Through Day 21	39 (93%)	31 (72%)	30 (71%)	81 (79%)	93 (90%)	85 (85%0

Safety:

Demographics: There were a total 505 patients with CHF who were exposed to Natrecor during the course of clinical development. There were additionally 24 patients who were exposed to Natrecor in one study

exploring the use of Natrecor in preventing post-CABG hypertension. Additionally, 258 patients were exposed to Nesiritide through studies culled from literature studies. The demographics are listed in Table Global –21.

The most pertinent data on Natrecor's safety comes from those exposed either to Natrecor or placebo during study #704.311; those exposed to Natrecor or placebo/standard therapy during study #704.325 or Natrecor versus standard therapy during study #704.326. This database contains information of 362 Natrecor treated and 173 placebo/standard therapy treated subjects and is the "long-infusion" data base cited in Dr. Throckmorton's review.

For the vast majority of subjects, the assessment of safety was done with knowledge as to the treatment (Natrecor versus standard therapy) but not necessarily with respect to the infusion dose of Natrecor.

Table Global-21: Demographics of that Enrolled into the Constant Infusion Studies (From Sponsor's Table Fax 2 February 1999)

Dose⇒	PBO/Standard Therapy	0.015* ug/kg/min	0.030* ug/kg/min	0.060 ug/kg/min
Total	173	169	167	26
Male	73%	71%	68%	88%
NYHA Class				
I	0 (0%)	0 (0%)	1 (1%)	0 (0%)
II	8 (5%)	8 (5%)	14 (8%)	2 (8%)
III	107 (62%)	97 (57%)	81 (49%)	15 (58%)
IV	58 (34%)	64 (38%)	71 (43%)	9 (35%)
Baseline Medications/Treatments:				
Diuretics	125 (72%)	126 (75%)	129 (77%)	16 (62%)
Digoxin	75 (43%)	87 (51%)	85 (51%)	8 (31%)
ACE-inhibitors	81 (47%)	100 (59%)	89 (53%)	15 (58%)
β-blockers	17 910%)	20 (12%)	9 (5%)	1 (4%0
Angiotensin II Blockers	9 (5%)	7 (4%)	9 (5%)	0 (0%)
AICD	3 (35)	2 (2%0	11 911%0	—
	(N=144)	(n=146)	(n=142)	
Concurrent Medical Problems**				
Previous MI	76 (53%)	78 (53%)	70 (49%)	Not
Chronic Renal Insufficiency	51 (35%)	45 (31%)	54 (38%)	collected**
Atrial Fibrillation/Flutter	62 (43%)	55 (31%)	55 (39%)	
History of Ventricular Tachycardia				
Non-sustained VT	32 (22%)	38 (26%)	35 (25%)	
Sustained VT	10 (7%)	7 95%)	18 (13%)	

* Populations were pooled based on infusion and not bolus regimens.
** Only collected for studies #704.325 and #704.326

Deaths: Duration of Treatment/Duration of Risk.

There were few subjects who died during the course of the study or during the stipulated follow-up period. The duration of follow up in study #704.311 was 15 days. For study #704.325 and #704.326 the stipulated follow-up time was 21 days. There were 9/173 (5.2%) patients who died on placebo/standard therapy and 18/362 (5.0%) on who died on Natrecor. There were five subjects lost to follow up; one in the standard therapy and four in the 0.015 ug/kg/min. Considering the number of subjects who died and the lack of knowledge as to the outcome of those lost to follow-up, there was no signal that Natrecor was either beneficial or detrimental to survival. Summaries of deaths are included in Dr. Throckmorton's review.

Hospitalizations: Hospitalization discharge rates, as well as re-hospitalization rates were tabulated in Table GLOBAL-20 for studies #704.325 and #704.326. There were an additional five subjects, all treated with Natrecor, who were either hospitalized or had prolonged hospitalization during Study #704.311. Given the small number of events and inconsistent outcomes across studies, no definitive conclusions can be made.

ADRs

Overall Safety: Dr. Throckmorton's review contains an excellent review of the overall safety of Natrecor. I've reproduced Dr. Throckmorton's summary as Table Global-22.

Table Global-22 Relationship of ADRs to Natrecor Treatment

Body System	Adverse Events:
Adverse Events Definitely, Probably or Possibly Linked to Natrecor Infusion	
Cardiovascular	Hypotension Bradycardia Decreased Pulmonary Pressures
Urogenital System	Renal Failure (Includes BUN and Creatinine Increases)
GI System	Nausea
Metabolic System	Hyponatremia Hyperglycemia/Hypoglycemia Hypermagnesemia Decreased Serum Total Protein and Albumin
Hemic and Lymphatic	Increased Hemoglobin, Hematocrit and RBC Count Increased WBC Count Increased Platelet Count
Adverse Events Unlikely to be Associated with Nesiritide	
Cardiovascular	Congestive Heart Failure Other Ventricular and Atrial Arrhythmias
Body as A Whole	Headache
GI Systems	Increased AST/ALT
Metabolic System	Hyper- and Hypo- kalemia
Hemic and Lymphatic	Allergic Reactions to Nesiritide
Musculoskeletal	Myalgias
Adverse Events For Which Data is Inadequate to Determine a Relationship with Nesiritide	
Cardiovascular System	ECG Abnormalities
Nervous System	Dizziness Nervousness
Urogenital System	Severe Renal Injury (Events leading to permanent loss of renal function)
Musculoskeletal System	leg Cramps
Hemic and Lymphatic	Sepsis Eosinophil Count
Special Senses	Amblyopia

Renal Function: Dr. Throckmorton's review makes a cogent case that renal function is adversely affected by Natrecor treatment. Discontinuations attributable to the urogenital system was limited to those who were treated with Natrecor (n=9) and these were most frequently listed as oliguria (n=5), creatinine increased (n=4) and acute renal failure (n=1). There were few subjects who required dialysis (these events could have occurred after the completion of the infusion but during the observation period) in the long infusion group and these subjects were fairly evenly distributed in both the placebo/standard therapy and Natrecor cohorts.

Prespecified levels of creatinine increases were more frequently encountered in Natrecor treated than in placebo/standard therapy treated subjects. Among those with asymptomatic or symptomatic hypotension, the frequency of creatinine rises of > 50% in studies #704.325 and #704.326 was 12/82 (15%) versus 23/217 (11%) among those without hypotension. (The relationship between hypotension and those with a 25% increase in creatinine was not submitted). The occurrence of hypotension was at best only a minimal factor in worsening renal function.

There is a modest signal for increase in urogenital/renal adverse events with dose. Most subjects who received standard therapy were treated with inotropes. Only approximately 18% were treated with