Medical Officer's Comment: *As stated above, the investigators did have the choice of decreasing the dosage of ciprofloxacin when sensitivity results were available. A review of NDA 19 – 847/S-8 revealed the following with regards to dosing:*

"Patients were dosed based upon their estimated creatinine clearance, and the antimicrobial susceptibility of the causative organism according to the following schedule":

CrCl	*A (Fully susceptible)*	*B (Moderately susceptible)*
> 70 mL/min	*Ciprofloxacin 400 bid* *Imipenem 500 q6*	*Ciprofloxacin 400 tid* *Imipenem 1g q8*
	Ciprofloxacin 400 bid *Imipenem 500 q8*	*Ciprofloxacin 400 tid* *Imipenem 500 q6*
	Ciprofloxacin 300 bid *Imipenem 500 q12*	*Ciprofloxacin 400 q12* *Imipenem 500 q8*
	Ciprofloxacin 250 q12 *Imipenem 250 q12*	*Ciprofloxacin 300 q12* *Imipenem 500 q12*

APPEARS THIS WAY ON ORIGINAL

All patients were started on schedule B or high dose and changes were made based on investigators clinical assessments. If renal insufficiency developed, an unblinded individual (research pharmacist) could have made dosage adjustments based on CrCl.

Although the protocol called for bacteriologic eradication at the early (3 –5 day post-therapy) follow-up to be the primary efficacy variable, the RMO disagreed and utilized clinical response as the primary efficacy variable. The RMO provided this analysis at both the early and late follow-up visits.

As per the RMO "For patients in both groups, almost all of the treatment duration was on regimen B; the mean duration of regimen B was 9.5 days for the ciprofloxacin group and 8.8 days for the imipenem, group (total mean duration of therapy was 10.5 days). 2% of the ciprofloxacin patients received regimen A only and 18% received both A and B. On the imipenem arm, 82% of patients received regimen B only, 1% regimen A only and 17% both. 76%of the clinically evaluable ciprofloxacin patients and 72% of the clinically evaluable imipenem patients received only the B regimen.

Based on the above information, the MO disagrees with the sponsor's contention that a significant number of patients received the lower dose. Clinical response rates for this trial were noted previously. The RMO did not provide a separate analysis of response by regimen.

The MO agreed with Pfizer's determination that ciprofloxacin dosage was adjusted for renal function. It is correct that 24% of the ciprofloxacin-treated patients had elevations of BUN during the study. There is no information available from the ciprofloxacin MOR as to how often dosage adjustments were made.

The sponsor states that no adjustments were made on the ciprofloxacin arms of the trovafloxacin studies. This is correct. However, it is merely speculative to assume that since adjustments were not made, that patients with creatinine elevations had by default higher ciprofloxacin doses, approximating the 400 tid level.

There is no evidence that the currently approved dose of ciprofloxacin for severe nosocomial pneumonia is superior to the previously approved dose

There are no studies comparing the efficacy and safety of twice a day IV ciprofloxacin with three times a day ciprofloxacin. In the absence of such studies, it is impossible to claim that the TID dosing (even if it had been consistently used in the pivotal study) is more effective than the BID

dosing, which was extensively used to treat nosocomial pneumonia for years. In any event, it is unlikely that any reasonably sized clinical trial could ever show a meaningful difference between the twice daily and three times daily dosing of ciprofloxacin in severe nosocomial pneumonia. It is generally believed that the underlying clinical condition is the most important driver for clinical outcome in this entity. In a disease where mortality is generally 20-60%, it is likely that such a clinical trial would have to be enormous (and clinically undoable) to show a difference in the two regimens.

Medical Officer's Comment: *Again the sponsor's response is speculative. Within the context of the ciprofloxacin SNDA there were 6 smaller studies (European), that indicated a clear increase in clinical success rates when progressively higher ciprofloxacin doses were utilized. These studies included many types of infections including NP. There are no large trials however that have compared the 2 regimens. Without a doubt however, ciprofloxacin 400 mg tid was studied in a well-designed trial within the context of the SNDA and was shown to be superior to a good comparator regimen.*

There are theoretical reasons to question the benefits of the dosing method used for ciprofloxacin in the pivotal study

Beyond a certain minimum level, there is no evidence in either ciprofloxacin studies or in the literature to show that progressively greater amounts of antibiotic result in progressively greater efficacy. Although it may be commonly believed (or at least practiced, even among some Infectious Disease specialists) that 'if some works, more is better', there is no evidence, for example, that antibiotic levels 20 times the MIC for an organism are more clinically efficacious than 10 times. Ciprofloxacin, like all quinolones concentrates 5-15 fold over serum levels in lung tissue, already giving levels at twice daily dosing that are substantially above those needed to kill most organisms.

If one were concerned about inadequate dosing, three times a day ciprofloxacin might not be any more effective than twice a day dosing. The three times daily dosing with 400mg does not result in substantially higher peak levels of antibiotic. Many people believe that with quinolones it is the peak level that is important for organism killing. From this viewpoint, to improve efficacy it would have made more sense to use a larger dose (i.e. 600mg individual dose, or more) rather than simply adding a dose. However, Bayer may have been concerned about the toleration profile, which appears to have been a concern with the original IV ciprofloxacin development and approval. In any event, there are no clinical data to show that three doses a day are more effective than two.

Medical Officer's Comment: *The MO is unaware of the argument of "more is better". The motivation behind the design of the ciprofloxacin SNDA is not in question at this time. As stated above, the regimen was efficacious. Any other conclusions drawn about the effectiveness of the higher dose regimen as opposed to the lower dose are merely speculative given the absence of additional clinical data.*

The primary rationale for the use of additional ciprofloxacin in the single pivotal study to support the 'severe nosocomial pneumonia' claim probably related to spectrum weaknesses and resistance issues that are irrelevant to the dosing used in the trovafloxacin study

It was, and remains a common belief in the medical community that a ciprofloxacin dose of 400mg BID is not adequate to treat *Streptococcus pneumoniae* infections, which was also the subject of an FDA advisory committee meeting. Indeed, under the 'lower respiratory tract infection' indication, the current package insert states that ciprofloxacin is not considered first line therapy for presumed or confirmed infections due to *Streptococcus pneumoniae*. We believe one of the primary reasons for the TID dosing in the pivotal study that Bayer used to claim severe nosocomial pneumonia was that they studied severe pneumonia, not exclusively nosocomial pneumonia, and included a large number of patients with community acquired pneumonia and potential Streptococcus pneumoniae infections. It is likely that investigators were very

uncomfortable with the prospect of treating patients with severe community acquired pneumococcal pneumonia with BID dosing.

There has also been concern over development of resistance during therapy with ciprofloxacin in nosocomial pneumonia, particularly with infections due to *Pseudomonas aeruginosa*. One thought has been that more antibiotic might reduce the incidence of resistance, apart from any effect on clinical efficacy. This was generally known to be a problem with ciprofloxacin dosed at 400mg twice daily, and it is likely that Bayer preferred that a higher dose of ciprofloxacin be used as monotherapy, rather than that a second (non-Bayer) antibiotic be added in an attempt to answer this criticism. Indeed, Bayer's interest in monotherapy with ciprofloxacin rather than combined therapy was the key design feature of the pivotal study. As this seems to be one of the few indications in infectious diseases where one can respectably advocate the use of more antibiotic rather than less, it is likely that Bayer was also quite comfortable with this approach. However, the primary use of monotherapy for pseudomonal pneumonia is in contrast to essentially all published recommendations for how severe nosocomial pneumonia should be treated, including those of the American Thoracic Society (2).

These issues driving a higher ciprofloxacin dose are not relevant to the trovafloxacin study. Since community acquired pneumonia was not enrolled, the presence of *Streptococcus pneumoniae* was not an issue for the ciprofloxacin arm. Additionally, Pfizer agrees with ATS that at least for infections due to *Pseudomonas aeruginosa*, dual therapy should be used, as was done in the #113 study. Although evidence that dual therapy improves clinical outcome is hard to come by, there is general consensus that at least it is useful to reduce development of resistance (2).

Medical Officer's Comment: *Once again the sponsor's comments are speculative and refer to the motivation of ciprofloxacin's sponsor. The MO agrees that ciprofloxacin is not first line therapy for CAP associated with Streptococcus pneumoniae. The MO points out however, that although the ciprofloxacin SNDA was intended to evaluate both CAP and NP, only 44/205 ITT ciprofloxacin patients actually had CAP. Thus the study was compromised mostly of patients with NP.*

The MO is unable to comment on Bayer's motivation to pursue the TID dosing. The MO disagrees with Pfizer's statement with regards to how NP should be treated. There is no clear documentation in the literature at this time with regards to the number of anti-microbials necessary to treat NP. Most commonly in clinical practice, more than one agent is utilized. This decision is clearly practitioner driven and based on a variety of factors such as severity of disease as well as local susceptibility and infection control issues.

There are other issues in the study that supported the use of ciprofloxacin in severe nosocomial pneumonia that detract from its strength:

--The study excluded patients with 'resistant' organisms, while the trovafloxacin studies did not.

--The primary endpoint was bacterial eradication and not clinical outcome.

--In the published report, it is very difficult to actually understand the analysis. For example, the intent to treat group excluded 25% of randomized patients for reasons that are not well explained.

--As noted above, there was considerable downward dose adjustment of ciprofloxacin that took place in the study, so that the significance of the higher dose is not clear.

--One of the stated rationales for the higher dose was the presence of resistant organisms (such as Pseudomonas aeruginosa) but one of the conclusions of the study was that dual therapy was needed for pseudomonal infections, thus drawing into question the reason for the higher dose.

--In spite of the above, the manuscript concluded that monotherapy was adequate, however the monotherapy hypothesis was not tested in the study, since both treatment arms were monotherapy regimens.

Medical Officer's Comment:

- *Patients in the ciprofloxacin SNDA could have been excluded if a resistant pathogen was isolated. This did not occur in the trovafloxacin trials. MO agrees with Pfizer.*

- *The primary endpoint as per protocol was bacteriologic efficacy and not clinical response. However, the RMO utilized clinical response at the EOS as the primary efficacy variable and the approval for ciprofloxacin in severe NP was based on these analyses.*

- *Approximately 25% of the randomized patients were excluded from the clinical trial for well-documented reasons. Specifically, of the 402 randomized patients, 229 were unevaluable for long term efficacy. The primary reasons for being unevaluable in the ciprofloxacin group were "no causative organisms" (30), "inadequate sputum specimens" (18), "resistant pre-therapy organisms" (20) , and "no EOS visit" (12).*

- *Pfizer's conclusion that there was considerable downward dose adjustment of ciprofloxacin is merely speculative.*

- *The sponsor's determination of the rationale of the study is also speculative. The conclusion in the ciprofloxacin SNDA was that ciprofloxacin was superior to the comparator in the treatment of severe NP, however, the subset of patients with Pseudomonas aeruginosa had lower eradication and clinical response rates. 33% of the isolates developed resistance on the ciprofloxacin arm as compared to 53% on the imipenem arm. The conclusion in the ciprofloxacin SNDA was that neither ciprofloxacin nor imipenem could be recommended as monotherapy for patients with Pseudomonas aeruginosa at least in the initial phase of treatment.*

- *The conclusion was that ciprofloxacin was effective as monotherapy with the exception of the aforementioned cases. It should be noted that the addition of IV vancomycin and metronidazole was allowed by-protocol and other antimicrobial usage was prohibited. This was generally adhered to.*

As true monotherapy, trovafloxacin may be superior to ciprofloxacin.

Because of the lack of anaerobic activity, additional blinded antibiotics (metronidazole or clindamycin) had to be added to the ciprofloxacin arm. Overall, in the two trovafloxacin studies of nosocomial pneumonia, 22% of patients on comparative agents received additional study antibiotics (aztreonam, vancomycin, clindamycin, metronidazole), while only 11% of trovafloxacin patients required additional antibiotics ($p<0.001$) (table 3.2 in study reports for #113 and #137). Additionally, there is a trend to less development of resistance by Pseudomonas aeruginosa in trovafloxacin recipients (see prior response regarding severe nosocomial pneumonia).

Medical Officer's Comment: *These data were presented previously. Certainly and as allowed by protocol, more patients received additional anaerobic coverage on the comparator arms. The MO does not disagree with the sponsor's statements although the conclusion that trovafloxacin is more effective as true monotherapy has not been adequately shown to the reviewer's satisfaction. The premise of monotherapy is to do away with the need for additional anaerobic and aerobic coverage.*

Conclusions

Ciprofloxacin was in fact previously approved for use in nosocomial pneumonia under the broader terminology of 'lower respiratory tract infections'. The original ciprofloxacin application contained pneumonia data drawn largely from nosocomial pneumonia patients, many of whom were severely ill by any criteria. Ciprofloxacin was broadly used to treat nosocomial pneumonia under the original indication and dosing. There is no evidence that the new dosing scheme has led to any clinical benefits.

As already noted, at the time that the trovafloxacin Phase 3 studies were designed and begun, neither ciprofloxacin, nor any other agent, were approved for nosocomial pneumonia, as such. Ciprofloxacin was clearly one of the most commonly used agents for treatment of nosocomial pneumonia, and after discussion with FDA, Pfizer elected to use it as a comparative agent at the dose then approved for treatment of "lower respiratory tract infection", which was a commonly

used dose for treatment of nosocomial pneumonia. Pfizer could not predict what approvals might occur in the future, and could have been criticized for using a larger than approved dose as an attempt to bias adverse event results or other factors such as convenience or cost in favor of trovafloxacin, as now the study is criticized for potential efficacy bias in favor of trovafloxacin for having used the approved and commonly used dose of the comparator. In spite of this, the data clearly show that trovafloxacin is effective in the treatment of severe nosocomial pneumonia, and may effect other advantages, such as simpler treatment regimens, less development of resistance, and reduced risk of drug interactions.

1. Fink MP, Snydman DR, Niederman MS, et. Al. Treatment of Severe Pneumonia in Hospitalized Patients: Results of a Multicenter, Randomized, Double-Blind Trial Comparing Intravenous Ciprofloxacin with Imipenem-Cilastatin. Antimicrob. Agents Chemo., Mar. 1994, Vol. 38, no. 3, p. 547-557.
2. Hospital-acquired Pneumonia in Adults: Diagnosis, Assessment of Severity, Initial Antimicrobial Therapy, and Preventative Strategies; A Consensus Statement. American Thoracic Society, Medical Section of the American Lung Association. Am. J. Respir. Crit. Care Med., 1995, vol. 153, p. 1711-1725.

Medical Officer's Conclusion: *The sponsor adequately demonstrated comparable efficacy with ciprofloxacin in a population of patients with severe NP as defined by ATS criteria.*

The issue of the adequacy of the comparator regimen and specifically the use of a lower dose of ciprofloxacin (400 bid) as opposed to the approved 400 mg tid was also addressed. The MO determined that the sponsor's response was primarily speculative with regards to ciprofloxacin's sponsor's motivation as well as with regards to the analyses of the results. The MO does not disagree with the sponsor that the dosage of ciprofloxacin utilized in the current trials was that which was approved at the time, however the higher dosage was that which received approval for the indication. This approval was granted while the trovafloxacin trials were ongoing.

The MO believes that an approval for severe NP should be issued only if trovafloxacin was found to be superior to the ciprofloxacin regimen. This however, was not the case. In the pivotal, blinded study, trovafloxacin was equivalent to ciprofloxacin but not superior. In study 154-137, trovafloxacin was numerically superior (statistical significance not achieved), to the ceftazidime/ciprofloxacin regimen however, that trial was an open study, and therefore the results may be biased. Equivalent efficacy in the severely ill subset was shown between trovafloxacin and the comparator regimens in both studies.

In the absence of clear superiority, the MO continues to recommend that trovafloxacin be approved for mild to moderate NP caused by Escherichia coli, Haemophilus influenzae, and Pseudomonas aeruginosa.

Pfizer's Recommendation for Nosocomial Pneumonia Indication Labeling for *Pseudomonas aeruginosa* Infections:

Pfizer believes the current statement in the proposed package insert regarding use of additional therapy in infections due to *Pseudomonas aeruginosa*, with minor modification, is the most appropriate approach and does not favor a statement that strongly directs a specific approach to medical therapy for several reasons:

There is little evidence in the literature and none in the trovafloxacin studies that dual therapy for nosocomial pneumonia due to *Pseudomonas aeruginosa* infections results in better clinical outcomes.

Indeed, in the trovafloxacin studies, the trend was in the opposite direction. To our knowledge, there is only a single report in the literature that shows dual therapy is clinically beneficial, and then only in bacteremic pseudomonal nosocomial pneumonia (1). Because there is no proof that additional therapy is beneficial in most cases of nosocomial pneumonia due to *Pseudomonas aeruginosa*, we do not believe a strongly directive statement is appropriate.

Medical Officer's Comment: *The MO agreed with the sponsor's statement regarding the dearth of evidence in the medical literature with regards to the requirement that dual therapy be utilized in patients with NP. The MO also agreed that in the trovafloxacin studies that no conclusions could be drawn as to*

the need for dual therapy in the subgroup of patients with NP caused by Pseudomonas aeruginosa. Clinical outcome was not affected either adversely or beneficially.

Package Inserts should reflect the data submitted that secured the approval:

Neither study #113 (trovafloxacin vs. ciprofloxacin) nor study #137 (trovafloxacin vs. ceftazidime) required additional antipseudomonal therapy at any time during the study. Indeed, protocol #113 prohibited additional therapy unless *Pseudomonas aeruginosa* was positively identified on a culture, and even in that case, it was left to the clinician's judgment as to whether additional therapy should or should not be added, depending upon all the factors present in these complex cases. Protocol #137 only allowed additional antipseudomonal therapy for identified cases in the comparative arm, although as noted in the study report, it was added in some cases to the trovafloxacin arm also. In fact, only about 50% of trovafloxacin patients who had *Pseudomonas aeruginosa* identified on a culture actually received additional antipseudomonal therapy in these studies. Those receiving the additional therapy did no better clinically than those who did not. Since the trovafloxacin studies did not require additional therapy, patients did not uniformly receive it, and patients did not demonstrably benefit when they did receive it, we do not believe a strongly directive statement is appropriate.

Medical Officer's Comment: *The MO reminds the reader that as per the study report of protocol 154 – 137 and the CRFs, 8 trovafloxacin-treated patients and 17 ceftazidime/ciprofloxacin-treated patients received adjunctive aminoglycosides when Pseudomonas aeruginosa was documented. 5/8 and 10/17 of these patients were clinically evaluable as per the sponsor. This is slightly more than 50% of the trovafloxacin patients. 4 of these cases were clinical failures.*

The MO agreed that patients with nosocomial pneumonia caused by Pseudomonas aeruginosa had conflicting results and that no definitive conclusions could be drawn.

There is no precedent in antibiotic package inserts for strongly directed practice recommendations unless they reflect actual study circumstances.

The only strongly directive package insert that we are aware of is for Zosyn, which states that "Initial presumptive treatment of patients with nosocomial pneumonia should start with Zosyn....PLUS AN AMINOGLYCOSIDE." It goes on to say that if *Pseudomonas aeruginosa* is not isolated, the additional therapy may be stopped. However, this statement simply reflects how the pivotal study was actually conducted. All patients received both Zosyn AND aminoglycoside from the initial dose, and it was a requirement that all patients with identified Pseudomonas aeruginosa continue the aminoglycoside (2). This approach seems to have been taken because an earlier study of Zosyn monotherapy failed, as mentioned in the package insert. This is quite different from the trovafloxacin studies. What is clear is that the original proposed statement for the trovafloxacin package insert is more specific and consistent with published guidelines (3) than that in any other package insert.

Medical Officer's Comment: *The MO agreed with the above with regards to the Zosyn® package insert.*

Package Inserts should not be used to direct medical practice in the absence of compelling medical evidence

The question of which medical practice is best for patients with nosocomial pneumonia, or a subset of these patients, is controversial, to say the least, and one best left to the larger medical community. It is in fact a controversial subject due to the lack of compelling data on which to base recommendations. Although the American Thoracic Society has published a consensus statement on this subject (3), the Infectious Disease Society of America has different views on a number of the issues, and is assembling another guideline (personal communication Lionell Mandell). We believe it would be a mistake to mandate a particular additional therapy, only to have that superseded by newer data or newer recommendations.

We believe that reminding physicians of the prerogative to use dual therapy in instances of nosocomial pneumonia due to *Pseudomonas aeruginosa* infection is useful and that this is appropriately accomplished with the original wording. However, we would have no objection to an added direct reference to the ATS Guidelines:

"NOSOCOMIAL PNEUMONIA caused by [organism list]. As with other antibiotics, treatment of nosocomial infections due to Pseudomonas aeruginosa may require combination therapy, as recommended in the American Thoracic Society consensus statement for treatment of hospital acquired pneumonia (3)."

1. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic Therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989, vol. 87, p. 540-546.

2. Zosyn Summary Basis of Approval.

3.Hospital-acquired Pneumonia in Adults: Diagnosis, Assessment of Severity, Initial Antimicrobial Therapy, and Preventative Strategies; A Consensus Statement. American Thoracic Society, Medical Section of the American Lung Association. Am. J. Respir. Crit. Care Med., 1995, vol. 153, p. 1711-1725.

Medical Officer's Comment: *The MO agrees with the sponsor that the labeling should contain information reflecting actual antimicrobial study circumstances. The outcomes in both protocols were conflicting and the numbers too small to be able to draw definite conclusions. The MO cannot advocate or disagree with the addition of a second agent in patients with nosocomial pneumonia due to Pseudomonas aeruginosa. However, the MO points out that trovafloxacin will be used in the empirical treatment of patients before culture results are available.*

The following statement drafted by the MTL, "Nosocomial pneumonia (mild to moderate) caused by Escherichia coli, Pseudomonas aeruginosa, or Haemophilus influenzae. As with other antimicrobials, where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated." most accurately reflects study circumstances as well as current medical opinion and should be added to the labeling in both the I and U section as well as the D and A.

On 12/9/97, additional analyses for the NP indication were requested to address whether trovafloxacin was superior in severely ill patients vs. the comparator arms. Specifically, it was requested that Pfizer provide clincial efficacy tables (EOS = TOC) for both studies separately and combined (Pfizer clinically evaluable population, severe patients only as defined by mutually acceptable ATS criteria), for patients with and without concomitant antimicrobial therapy (all concomitant antimicrobial agents, including clindamycin, metronidazole, vancomycin, aztreonam and aminoglycosides). The question as expressed by this request: "Was trovafloxacin alone superior to ciprofloxacin/comparator alone or in combination with other agents in patients with severe disease only?"

This information was provided by the sponsor on 12/9/97 in the form of several tables sent by FAX. These tables were combined into the table below and revealed the following:

Nosocomial Pneumonia Pfizer Clinically Evaluable Population at EOS Severe Disease ONLY by ATS Criteria							
		154 –113 (US) (vs. Ciprofloxacin IV 400 bid→PO Ciprofloxacin 750 bid)		154 – 137 (Europe) (vs. Ceftazidime 2 gm IV bid→ PO Ciprofloxacin 750 bid)		Combined Studies	
		No. Cured/No. Eval	(%)	No. Cured/no. Eval	(%)	No. Cured/No. Eval	(%)
Trovan	Monotherapy	28/46	61	33/54	61	61/100	61
	Adjunctive	7/10	70	1/7	14	8/17	47
	Both	35/56	63	34/61	56	69/117	59
Comparator	Monotherapy	32/48	67	33/53	62	65/101	64
	Adjunctive	4/9	44	2/12	17	6/21	29
	Both	36/57	63	35/65	54	71/122	58

95% CI with CCF (d = 20)
Study 154 –113:
Trovan Monotherapy vs. Ciprofloxacin Monotherapy: - 27%, 15.7%
Trovan Both vs. Ciprofloxacin Both: - 20.2%, 19%

Study 154 – 137:
Trovan Monotherapy vs. Ceftazidime/Ciprofloxacin Monotherapy: - 21.4%, 19%
Trovan Both vs. Ceftazidime/Ciprofloxacin Both: - 17.1%, 21%

Combined:
Trovan Monotherapy vs. Comparators Monotherapy: - 18%, 11%
Trovan Both vs. Comparators Both: - 12.5%, 14%

The MO requested that the sponsor provide line listings of the patients included in the adjunctive categories in the above table. These were faxed on December 11, 1997 and revealed the following:

In study 113: 7/10 (70%) trovafloxacin patients received aztreonam (2 failures, 5 cured or improved), 4/10 (40%) trovafloxacin patients received vancomycin (1 failure, 3 cured or improved), and none of the trovafloxacin patients received adjunctive anaerobic coverage. Only 1 of these patients received both vancomycin and aztreonam and that patient was improved at the EOS.

On the ciprofloxacin arm, only 1/9 (11%) patients received aztreonam and was a failure. This patient also received clindamycin. 2/9(22%) patients received vancomycin and both were failures. One of these patients also received clindamycin. 6/9 (66%) patients received clindamycin and in addition to the 2 aforementioned failures, 2/6 were failures (or 4 total failures) and 2/6 (22%) were cured.

In study 137: 4/7 (57%) trovafloxacin patients received gentamicin (3 failures and 1 cured), 4/7 (57%) received vancomycin (all failed), and no patient received additional anaerobic coverage. Only one of these patients received both gentamicin and vancomycin and was a failure.

On the ceftazidime/ciprofloxacin arm, 8/12 (67%) patients received gentamicin (6 failures and 2 cured), 6/12 (50%) received vancomycin (5 failures and 1 cured), and none of the patients received additional anaerobic coverage. There were 2 patients who received both gentamicin and vancomycin (1 failure and 1 cured).
Medical Officer's Comment: *Very similar numbers of patients from both studies combined received monotherapy versus concomitant therapy. Interestingly, only 1(11%) patient on the ciprofloxacin arm of study 113 received additional antipseudomonal coverage as opposed to 7 or 70% of the trovafloxacin patients. The main difference in study 113 was the addition of anaerobic coverage in 67% of the ciprofloxacin patients and none of the trovafloxacin patients. However, in study 154 – 137, none of the*

severely ill patients on either arm received anaerobic coverage. Similar numbers of patients on both arms received gentamicin and vancomycin.

The 95% CI for the monotherapy patients in study 154 –113 with severe NP indicated that trovafloxacin was NOT equivalent to ciprofloxacin. Additionally, equivalence was not demonstrated when all severe trovafloxacin patients, any mode of therapy were compared to all severe ciprofloxacin patients, any mode of therapy. Equivalence was also not demonstrated for monotherapy in study 154 –137. In both studies combined, trovafloxacin monotherapy was equivalent to comparators monotherapy. Equivalence was also demonstrated in trovafloxacin patients with severe disease, combination therapy versus ceftazidime/ciprofloxacin combination therapy in study 154 –137, as well as in both studies combined.

Initially it appeared as if there was some superiority of trovafloxacin adjunctive therapy in both studies versus the adjunctive therapy comparators both studies, that is 47% versus 29%. However the numbers are too small 7/18 versus 6/21 to be able to detect any real difference.

From the above, the MO was unable to detect any superiority of trovafloxacin monotherapy versus comparators either as monotherapy or in conjunction with adjunctive antimicrobial therapy. Indeed, equivalence was not shown between trovafloxacin monotherapy and ciprofloxacin monotherapy in the pivotal US study or the open European study for severe NP. However, when the studies were combined, equivalence was demonstrated.
The above table was emailed to the sponsor on 12/10/97 for further comment with regards to trovafloxacin's claim of superiority as a monotherapeutic agent versus ciprofloxacin in the treatment of severe (as defined by ATS criteria) nosocomial pneumonia.

***Medical Officer's Conclusion**: The sponsor was unable to adequately demonstrate that trovafloxacin monotherapy was superior to ciprofloxacin monotherapy or combination therapy or both combined in the severely ill (as defined by ATS criteria) population. Trovafloxacin combination therapy was equivalent with the comparators combination therapy in study 154 – 137 and with all studies combined but not equivalent with ciprofloxacin combination in the pivotal US study.*

The question of the adequacy of the comparator regimen becomes moot in the face of these analyses. If trovafloxacin was unable to meet the 95% CI at a lower than approved dose of ciprofloxacin for severe NP, then the issue of the use of the appropriate dose raises questions as to the efficacy of trovafloxacin for the indication itself.

Based on the above, the MO does not recommend approval for trovafloxacin in patients with severe nosocomial pneumonia.

On, December 12, 1997, the sponsor submitted a document entitled "Further Comments on Inclusion of *Staphylococcus aureus* and *Klebsiella pneumoniae* in Nosocomial Pneumonia and Community Acquired Pneumonia Indications" in which the sponsor presented further arguments as to why *Staphylococcus aureus* and *Klebsiella* pneumoniae are legitimate organisms for both of these indications and that sufficient data are available to include them. Portions of the sponsor's arguments are appended below:

Staphylococcus aureus:

–In Nosocomial pneumonia alone, there were 21 *Staphylococcus aureus* isolated and 14 successfully clinically treated at EOS (67%) in the two trovafloxacin protocols, results equal to the overall outcomes. The figures for the comparators are 10/21 (48%). The somewhat better efficacy with trovafloxacin is not surprising since trovafloxacin is at least an order of magnitude more active than ciprofloxacin or ceftazidime. In CAP, 18/18 were successfully treated in the trovafloxacin arms.

–*Staphylococcus aureus* was included in the levofloxacin CAP indication, apparently on the basis of successful outcomes in 15/17 cases, as reported in the clinical trials section of the package

insert. As noted below however, the levofloxacin CAP studies were very weak in key design areas (one was unblinded and the other non-comparative).

--*Staphylococcus aureus* was included in the recent Zosyn® label for Nosocomial pneumonia apparently on the sole basis of organisms acquired in the single pivotal trial vs. ceftazidime in which 155 patients were randomized to Zosyn®. From the medical officer's review (p. 75), it is apparent that approval was gained on the basis of 13 successful courses out of 16 isolates.

--We regard this as a 'level playing field' issue. We believe we have studied adequate numbers that are at least equal to those studied in recent approvals. We do not believe the sponsors of levofloxacin and Zosyn® were required to specially 'prove the validity' of this particular isolate as Pfizer was, for an organism that is generally regarded as a pathogen in these infections.

Medical Officer's Comment: *The MO determined that the information presented above refers to 2 different indications, that is NP and CAP. With regards to NP, the MO found a combined clincial response rate of 12/19 (63%). The MO's rate is slightly lower that that of the sponsor, however, this rate is superior to that found in the ciprofloxacin NDA 19 – 847/S-3 for severe NP: 8/14 (57%). As noted previously, ciprofloxacin did not obtain an approval for this isolate in severe disease.*

With regards to the Zosyn® NDA 50 –684, the MO noted previously, that an approval was granted based on an eradication rate (EOS) of 13/16 (81%).

The MO determined that the levofloxacin data for the CAP indication are not pertinent to the current indication. A previous divisional decision stated that it would be inappropriate to extrapolate data form a more severe indication to a lesser severe.

Nevertheless, the MO agreed with the sponsor with regards to the adequacy of the data presented in the trovafloxacin submission. Certainly, this submission contained adequate information to grant an approval for this isolate in patients with mild to moderate NP only. The MO clarifies this issue because the data from the Zosyn® NDA, despite being obtained from a single clinical trial, were obtained from a severely ill population and the cure rate was higher than that of trovafloxacin. Additionally, as per the MO's data, the comparators in the ciprofloxacin NDA 19-847/S-3 had a combined clincial response rate of 10/15 (67%).

As per the sponsor:
Klebsiella pneumoniae

--Across nosocomial pneumonia and CAP, 18/24 *Klebsiella pneumoniae* isolates were successfully treated. Eight were from Nosocomial pneumonia with 4 clinical successes, while 16 were from double blind, randomized, controlled trials in CAP, with 14/16 successfully treated (EOS). From p. 407 of the medical officer's review of levofloxacin, it appears that there were only 6 clinically evaluable subjects with this isolate, several of which appear to have originated in the non-comparative trial #M92-075. The medical officer did not recommend approval for this organism, however, there is a reference on p. 427 to additional data from supportive trials in an 'addendum', which is not available to Pfizer.

--The only other recent reference to *Klebsiella pneumoniae* is the levofloxacin package insert clinical trials section, where a figure of 10 isolates, all successfully treated, is cited.

--We regard this as a 'level playing field issue'. The primary source of the *Klebsiella pneumoniae* for the levofloxacin label was from an unblinded study (vs. ceftriaxone/cefuroxime) which was justly criticized by the medical officer because of this and other deficiencies. The only further data seem to have come from a non-comparative study, as reported in the clinical trials section. The trovafloxacin CAP data on *Klebsiella pneumoniae* are from much more robust double blind studies. More *Klebsiella pneumoniae* were studied in the trovafloxacin CAP program, by a considerable margin than in the levofloxacin program.

--The agency may fairly take the position that it has made an egregious error in the levofloxacin label and will not include organisms on such flimsy data in the future. However, the trovafloxacin data are much more robust and much greater in quantity. To not include *Klebsiella pneumoniae* would be unfair.

Medical Officer's Comment: *As per the MO and the sponsor the clincial response rate by pathogen for Klebsiella pneumoniae was 4/8 (50%). both studies combined in NP. The MO determined that this rate was very low compared with that of ciprofloxacin in NDA 19 – 847/S-3: 8/9 (89%). The MO as noted above, determined in conjunction with the Division, that it would be inappropriate to extrapolate data from a less severe indication (CAP), to a more severe (NP).*

Based on the above, the MO continues to recommend a non-approval for this organism in NP.

Medical Officer's Overall Conclusion:

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Based on all the data reviewed and after labeling discussions with the sponsor on 12/18/97, the MO agreed to recommend approval for trovafloxacin in the treatment of NP without referring to severity. This decision was made because of the equivalent efficacy between trovafloxacin and the comparator agents in both clinical trials for the overall populations. The sponsor agreed to a Phase 4 commitment

RECOMMENDED REGULATORY ACTION:

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The following statement should be added to the Indications and Usage section of the labeling:

Additionally, this statement should be added to the Dosage and Administration section. The approved dose is alatrofloxacin/trovafloxacin 300 mg IV to 200 mg PO daily for 10 –14 days.

A clinical studies section describing the results of the US trial is recommended.

/S/ 12/19/97
Regina Alivisatos, MD
Medical Officer, DSPIDPs

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Orig. NDA #20-759
Orig. NDA #20-760
HFD-590 /S/
HFD-590/Div. Dir./MGoldberger
HFD-590/Dep. Dir./RAlbrecht
HFD-590/MTL/BLeissa /S/ 12/17/97
HFD-590/MO/RAlivisatos
HFD-590/CSO/PFogarty
HFD-725/Biostat/Silliman
HFD-344/Thomas

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ON ORIGINAL

Appendix I/NDA 20 – 759

List of Investigators and Study Sites (Copied from the Esub):

Uncomplicated UTI/154-103:

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5003 James McCarty, MD.	Richard Ascoli, MD Katherine Baker, RA R. Wayne Ball, MD Andrea Brauninger, MD Burt Cochran, MD Joann Crawford, RN Diane Dubose, MA Barbara Fragale, RN M. Gail Gallagher, NP Cathy Good, RN Karen Heesch, RN Yvette Hernon, RN Jeanne Kokes, RN Margaret Northrop, RN Juan Patlan, PA Josie Regalado, MA Antonio Renteria, RN Gloria Rodriguez, MA Sharon Zarcone, LPN	California Medical Research Group 3636 North First Suite 120 Fresno Ca 93726 Cal Poly State University Cal Poly Health Services San Luis Obispo, Ca 93407
5005 Willis Manford Gooch, III, MD.	Terese Cracroft, RN Daniel Davis, MD John Herrod, MD Spencer Jones, MD Tina Kerr, LPN Darla Longhurst, MD Rodney Marriot, MD Kenneth Nielson, MD Cheryl Ritchie, RN Mark Shepherd, MD Larry Staker, MD Jennifer Tower	Medical Research Associates Of Utah Incorporated 265 East 100 South, Suite 255 Salt Lake City, Ut 84111 Bryner Clinic 745 East 300 South Salt Lake City, Ut 84102 St. Benedict's Women's Center, 5495 South 500 East Washington Terrace, Ut 84405
5006 Corey Tancik, MD	Barbara McGuire, MD William Mitchell, MD Jeffrey Sollins, MD Lori Spragg, MA David Stryker, MD Barbara Wright, RN	New Mexico Medical Group 8324 Constitution Place Northeast Albuquerque, NM 87110 Kiva-New Mexico Medical Group Pc-2, 8324 Constitution Place Northeast Albuquerque, NM 87110
5008 Stephen Gordon, MD	Lawrence Goldstone, MD Sally Jay, PAC Jeanne Lunsford, RNC	Future Healthcare Research Center 975 Johnson Ferry Road Suite 370 Atlanta, GA 30342 Atlanta Northside Center For Women 980 Johnson Ferry Road Suite 350, Atlanta, GA 30342

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

5009 Robert Bedinger, Jr, MD	Joseph Galeski, III, MD Katherine Smallwood, MD Neshan Vranian, MD	The Mcguire Clinic Incorporated 7702 Parham Road Richmond, VA 23294
5010 Caryn Nesbitt, MD.	Carol Carilli, RN Ruth Donahue, MD Catharine Moffett, RN Diane Morgenthaler, MD	Women's Care Medical Center 85 Poheganut Road Groton Business Park Route 117 Groton, CT 06340
5011 Anthony Puopolo, MD.	Robert Chiulli, MD David Getz, MD Bruce Karlin, MD Mark Lemons, MD	5 Water Street Milford, MA 01757; 270 High Street Clinton, MA 01510
5012 Z.A. Dalu, MD	Virginia Abu Dalu, RN	100 North Euclid Suite 710 St Louis, MO 63108
5013 Larry Gilderman, DO.	Gary Blumberg, DO Aleyda Borge, MD	University Clinical Research 1150 North University Drive Pembroke Pines, Fl 33024
5014 Ira Klimberg, MD		Urology Center Of Florida 3201 Southwest 34th Street Ocala, Fl 34474
5017 John Gezon, MD.	James Antinori, M.D. Kathy Atkinson, MD Daniel Duggleby, MD Robert Gannon, MD Lance Owens, MD Marcia Prather, MD Michael Romney, MD	1388 Arlington Drive Salt Lake City, Ut 84103 Holy Cross Hospital 1050 East South Temple Salt Lake City, Ut 84102
5040 Theodore Appel, MD	Daniel Austin, MD Carole Christensen, MD Peter Earl, MD John Imig, MD Marlene Kaniuk, MD Sherbune Macfarlan, MD	Boulder Medical Center Research Department 2750 Broadway Boulder, CO 80304
5041 Robert Fiddes, MD	Julian Fuentes, MD	Southern California Research Institute 12291 East Washington Boulevard Suite 204 Whittier, Ca 90606
5042 Joseph Scott, MD	Sara O'Heron, MD Harvey Resnick, MD Irvin Sabrsula, MD	R/D Clinical Research Incorporated 135 Oyster Creek Drive Suite V Lake Jackson, TX 77566
5043 Daniel Wermeling, Pharm. D.	Norman Goodman, Ph.D Susan Griffith, MD Larry Munch, MD David Wood, MD	University Of Kentucky College Of Pharmacy Rose Street Room 319 Lexington, KY 40536-0082 University Of Kentucky Medical Center 800 Rose Street Lexington KY 40536; Veterans Administration Hospital Cooper Drive Lexington, KY 40511
5044 Charles Jenkins, MD	Lawrence Repsher, MD	3550 Lutheran Parkway West Suite G-20 Wheat Ridge, Co 80033

Study 154 –116/Uncomplicated UTI:

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5003 Jose Ibarra, M.D. James McCarty, M.D.	Ariya Abraham, M.D. Richard Ascoli, M.D. R. Wayne Ball, M.D. Nancy Bliele, M.D. Hani Boutros, M.D. Andrea Brauninger, M.D. Julian Carabeth, M.D. Burt Cochran, M.D. Frank Mazzone, M.D. Anthony Molina, M.D. Juan Patlan, P.A.-C. Thomas Richards, M.D. Parimal Shah, M.D. Anila Thampy, M.D.	Future Healthcare Research Center 3636 North First Street #120 Fresno, CA 93726 California Poly Technic State University Student Health Services San Luis Obispo, CA 93407 San Luis Obispo Family Practice 47 Santa Rosa San Luis Obispo, CA 93405
5005 Willis Gooch, III, M.D.	Daniel Davis, M.D. John Herrod, M.D. Ann Jefferds, M.D. Spencer Jones, M.D. Kenneth Nielson, M.D. Keith Pearson, M.D. Dorene Sambado, M.D. Mark Shepherd, M.D. John Smith, M.D. Lorraine Szczesny, M.D.	Medical Research Associates of Utah, Inc. 265 East 100 South, Suite 255 Salt Lake City, UT 84111 Bryner Clinic 745 E. 300 South Salt Lake City, UT 84102 Umap Clinic 250 E. 300 S. 200 Salt Lake City, UT 84111 Medical Associates of Salt Lake 508 E. S. Temple, Suite 300 Salt Lake City, UT 84102
5011 Anthony Puopolo, M.D.	Aly El-Hag, M.D.	5 Water Street Milford, MA 01757
5013 Larry Gilderman, D.O.	Aleyda Borge, M.D. Jose Molina, P.A.	1150 North University Drive Pembroke Pines, FL 33024
5041 Robert Fiddes, M.D.	Peter Arcan, M.D. Julien Fuentes, M.D.	12291 East Washington Blvd. Whittier, CA 90606
5138 Randall Stoltz, M.D.	Patrick Flamion, M.D. Bryan Laura, M.D. Richard Murray, M.D. Ward Neff, M.D. Raymond Newnum, M.D. John Polin, M.D. Jennifer Wahle, M.D.	GFI Pharmaceutical Services Inc. 800 St. Mary's Drive Evansville, IN 47714
5468 Hendrik Mulder, M.D.	Jacobus Koster, M.D. Lennie Van Setten Van Der Meer, R.N.	Medisch Onderzoekscentrum Gcp Groot Hertoginnelaan 34 N1-2517 Eh Den Haag The Netherlands

5492 Nicholas Creel, M.D.	Alkesh Amin, M.D. Donald Bennett, M.D. Gerald Bottenfield, M.D. Raymond Jess, M.D. Sara O'Heron, M.D. Ronald Paul, M.D. Harvey Resnick, M.D. Irvin Sabrsula, M.D. Joseph Scott, M.D. Roberto Ticas, M.D.	R/D Clinical Research Inc. 135 Oyster Creek Drive Suite W, Suite V, Suite S Lake Jackson, TX 77566 201 Oak Dr. South, Suite 107 Lake Jackson, TX 77566 201 Oak Dr. South, Suite 202 Lake Jackson, TX 77566 215 Oak Dr. South, Suite A Lake Jackson, TX 77566 56 Flag Lake Plaza Lake Jackson, TX 77566 201 Oak Dr. South, Suite 203 Lake Jackson, TX 77566 146 Hospital Drive, Suite 102 Angleton, TX 77515 215 Oak Dr. South, Suite B Lake Jackson, TX 77566
5630 Ronald Castellanos, M.D.	James Borden, M.D. Paul Bretton, M.D. William Evans, M.D. Ronica Kluge, M.D. Sergio Mather, M.D. David Mitchie, Ph.D. Jasper Rizzo, M.D. Mary Yankaskas, M.D. Stephen Zellner, M.D.	12651 Whitehall Drive Fort Myers, FL 33907 Clinical Physiology Associates Clinical Study Center 4110 Center Pointe Drive, Sute 219 Fort Myers, FL 33916 Southwest Florida Urologic Associates 12651 Whitehall Drive Fort Myers, FL 33907 Southwest Florida Urologic Associates 507 Del Prado Boulevard Cape Coral, FL 33990 Gulfshore Obstetrics and Gynecology 12631 Whitehall Dr. Fort Myers, FL 33907 Internal Medicine Associates 2675 Winkler Ave., Suite 300 Fort Myers, FL 33901

5632 Ronald Gove, M.D.	Peter Costantini, D.O. Alan Feldman, M.D.	Jersey Research Foundation Inc. 1001 North Main St. Pleasantville, NJ 08232 Jersey Research Foundation, Inc. 222 New Road Linwood, NJ 08221 Jersey Research Foundation, Inc. 53 West White Horse Pike Absecon, NJ 08201
5633 Gholam Malek, M.D.	Percy Golson Andrew Graf, M.D. Michael Kuglitsch, M.D. John Mahler, M.D. John Wegenke, M.D.	Jackson Foundation Physicians Plus 345 West Washington Ave. Madison, WI 53703 Physicians Plus Medical Group 20 South Park St. Madison, WI 53715
5635 Marcia Montgomery, M.D.	Bryan R. Kurtz, M.D. Raoul Concepcion, M.D. Cynthia Lee Shearer, M.D.	2222 State Street, Suite D Nashville, TN 37203 Clinical Research Associates, Inc. 2222 State Street, Suite D Nashville, TN 37203 2400 Patterson Street, Suite 204 Nashville, TN 37203
5636 Stuart Sarshik, M.D.		Urology Associates 2011Church St., Suite 600 Nashville, TN 37203 2021 Church St. Nashville, TN 37203 711 Lawn Ave., Building 1 Sellersville, PA 18960 Grand View Hospital 700 Lawn Ave. Sellersville, PA 18960 Pennridge Urological Associates 670 Lawn Ave. Sellersville, PA 18960
5637 Alan Tice, M.D.	Philip Craven, M.D. Peter Marsh, M.D. David McEniry, M.D. Lawrence Schwartz, M.D. Catherine Treseler, M.D.	Infections Limited PS 1624 South I Street 402 Tacoma, WA 98405

APPEARS THIS WAY
ON ORIGINAL

5681 Abdollah Iravani, M.D.	John Langton, M.D.	Central Florida Medical Research Center 1720 South Orange Ave., Suite 401 Orlando, FL 32806
		University of Central Florida (UCF) UCF Student Health Services 400 Central Florida Blvd., Bldg. 27 Orlando, FL 32816
5733 Ellen Guthrie, M.D.	John Corkery, M.D. John Crites, M.D. Margaret Cronin, M.D. Bessann Dawson, M.D. Franzisca Garrett, M.D. Deepa Gupta, M.D. Dennis Kay, M.D. Gary McFadden, M.D. Adrian Milea, M.D. Karen Neal, D.O. Mark Passey, M.D. Leonard Portocarrero, M.D. Drew Schembre, M.D. Kathleen Tucker, M.D. Alan Whitesides, M.D.	Advanced Clinical Research 34 South 500 East 102 Salt Lake City, UT 84102 Rose Park Insta Care 55 North Redwood Rd. Salt Lake City, UT 84116 Bountiful Insta Care 214 West 1500 South Bountiful, UT 84010 Holladay Insta Care 3934 South 2300 East Salt Lake City, UT 84124 Sugar House Insta Care 2915 South 700 East Salt Lake City, UT 84106
5783 Philippe Angeli, M.D.		1 Residence Les Roses Rouges 155 Rue De Chevilly 94800 Villejuif France
5784 Marc Hindamian, M.D.		19 Avenue Raspail 94250 Gentilly France
5785 Max Labyod, M.D.		32 Avenue Paul Doumer 94110 Arcueil France
5786 Jacques Sultan, M.D.	Toledano, M.D.	Groupe Medical De La Mairie 5 Place De L'Eglise 94260 Fresnes France
5787 Sylvaine Dumas, M.D.		61 Avenue De Paris 94800 Villejuif France
5790 Gosta Granberg, M.D.	Manochehr Nezami	Kvinnokliniken Centrallasarette I Boden S-961 85 Boden Sweden Kvinnokliniken Lulea Lasarett 971 25 Lulea Sweden

5791 Elisabeth Weiner, M.D.	Ann-Marie Terner, M.D.	Brickegardens Vardcentral Osterleden 10 S-691 81 Karlskoga Sweden
5792 Anders Henriksson, M.D.	Inger Aurell, M.D. Agneta Moller, M.D.	Specialistlakarhuset Hermelinen Box 195 S-971 06 Lulea Sweden
5793 Leif Weiner, M.D.		Medicinkliniken Karlskoga Lasarett S-691 81 Karlskoga Sweden
5794 Bengt Widgren, M.D.	Bengt Persson, M.D.	Department of Medicine Sahlgrenska Sjukhuset S-413 45 Goteborg Sweden
5797 Roland Weil, M.D.		Habichstr 10 75175 Pforzheim Germany
5798 Reinhard Schorten, M.D.		Schleibheimstr 77 85221 Dauchau Germany
5799 Christian Saul, M.D.		Nymphenburger Str 59 80335 Munchen Germany
5801 Jens Herold, M.D.		Leopoldstr 71 80802 Munchen Germany
5802 Constantin Aurel Baran, M.D.		Troppenauerstr 8c 85221 Dauchau Germany
5803 Hendrik Mulder, M.D.	H. Christiaanse Pauline De Graaf-Pernot Mrs. Edcius Pieternella Van Wendel De Joode	Medisch Onderzoekscentrum Gcp Walenburgerweg 33 N1-3039 Ac Rotterdam The Netherlands Medisch Onderzoekscentrum Gcp Bergweg 66 N1-3036 Bc Rotterdam The Netherlands
5804 Hans Prak, M.D.	Bernardina Prak-Holtzing	Rembrandtlaant3 N1-9581 Aj Musselkanaal The Netherlands
5821 Harry Fransen, M.D.	A. Oost-Buurman	Marktstraat 70 N1-9581 Ad Musselkanaal The Netherlands

Study 154 –117/Complicated UTI:

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5005 Willis Gooch III, MD	Daniel Davis, MD John Herrod, MD Ann Jefferds, MD Spencer Jones, MD Kenneth Nielson, MD Keith Pearson, MD Dorene Sambado, MD Mark Shepherd, MD John Smith, MD Lorraine Szczesny, MD	Medical Research Associates of Utah, Inc. 265 E. 100 South Suite 255 Salt Lake City, UT 84111 Bryner Clinic 745 E. 300 South Salt Lake City, UT 84102 UMAP Clinic 250 E. 300 South Suite 200 Salt Lake City UT 84111 Medical Associates of Salt Lake 508 E. S. Temple Suite 300 Salt Lake City UT 84102
5034 Guillermo Rodriquez, MD	Celia Barrantes Howay, MD Katy Barrantes Jimenez, MD Andrea Bianchi, MD Sofia Gonzalez Ugalde, MD Jorge Mora Duarte, MD Iris Perez Quiros, MD	Hospital Mexico 3er Piso Biblioteca Medica San Jose Costa Rica Hospital Calderon Guardia PO Box 10105 San Jose, Costa Rica Hospital San Juan De Dios PO Box 10105 San Jose, Costa Rica Centro Nacional De Rehabilitacion (Cenare) PO Box 10105 San Jose, Costa Rica
5078 C. Andrew Deabate, MD	Victor Brown, MD J. Craig Cornett, MD	Medical Research Center 1020 Gravier Street New Orleans, LA 70112 3600 Prytania St. Suite 100 New Orleans, LA 70115 Medical Research Center 3655 Veteran's Boulevard Metairie, LA 70002 1020 Gravier St. New Orleans, LA 70112 Waldon Healthcare Center 2401 Idaho Kenner, LA 70062

5138 Randall Stoltz, MD	Patrick Flamion, MD Bryan Laura, MD Richard Murray, MD Ward Neff, MD Raymond Newnum, MD John Polin, MD Jennifer Wahle, MD	GFI Pharmaceutical Services, Inc. 800 St. Mary's Drive Evansville, IN 47714
5606 Robert Gainer, MD	T. Edward Blume, MD Robert Curtis, MD Suzanne Gainer Alan Hess, MD Timothy Nelms, MD Norval Rasussen, MD Jeffrey Sinclair, MD	Morgantown Internal Medicine Group, Inc. 300 Wedgewood Dr. Morgantown, WV 26505 Monongalia General Hospital 1200 JD Anderson Dr. Morgantown, WV 26505
5639 Stephen Auerbach, MD	Ronald Gilbert, MD Richard Holevas, MD John Ravera, MD Joel Sheiner, MD Ronald Solomon, MD Don Udall, MD	400 Newport Center Dr. Suite 501 Newport Beach, CA 92660 1401 Avocado Ave. Suite 608 Newport Beach, CA 92660 1901 Westcliff Dr. Suite 2 Newport Beach, CA 92660 16912 Sims St. Suite 203 Huntington Beach, CA 92649 351 Hospital Dr. Suite 516 Newport Beach, CA 92663 1401 Avocado Ave. Suite 602 Newport Beach, CA 92660
5640 Bruce Blank, MD	Jack Brewer, MD Romney Burke, MD Jerry Giesy, MD Michael Kaempf, MD Theodore Lehman, MD Gregory McCoy, MD Patrick Ohollaren, MD Walter Reynolds, MD David Winchester, MD	Urology Clinic PC 1130 Northwest 22nd Ave. Suite 620 Portland OR 97210 The Urology Clinic 501 N. Graham Suite 420 Portland, OR 97227 1400 Division St. Suite 1 Oregon City, OR 90745

APPEARS THIS WAY
ON ORIGINAL

5641 Howard Rottenberg, MD	James Brigman, MD Douglas Nyhoff, MD Harvey Tauber, MD	North Atlanta Urology Associates PC 5671 Peachtree Dunwoody Road Suite 300 Atlanta GA 30342
		Nucare Clinical Trials, Inc. 3400 McClure Bridge Rd. Duluth GA 30136
5642 Stanley Brosman, MD	Matteo Dinolfo, MD Stuart Fisher, MD Ian Gale, MD David Leff, MD Richard Leff, MD Ronald Nudelman, MD James Orecklin, MD	Santa Monica Urological Medical Group 1260 15th St. Suite 1200 Santa Monica, CA 90404 Santa Monica Urological Medical Group 1260 15th St.
	Robert Saffian, MD Arthur Schapiro, MD Richard Shapiro, MD Leonard Skaist, MD	Suite 709 Santa Monica CA 90404 San Fernando Valley Urologic Associate Medical Group Inc. 18370 Burbank Blvd. Suite 407 Tarzana CA 91356
		7345 Medical Center Dr. Suite 300 West Hills CA 91307
5644 Raoul Concepcion, MD	Jon Levine, MD Marcia Montgomery, MD Richard Pinson, MD	Clinical Research Associates 2222 State St. Suite D Nashville TN 37203
		Urology Associates 2011 Church St. Suite 600 Nashville TN 37203
		2400 Patterson St. Suite 204 Nashville TN 37203
5645 Clair Cox, MD	Anthony Patterson, MD	University of Tennessee Dept. of Urology 956 Court Ave. Room H-216 Memphis TN 38163
5647 Robert Feldman, MD	Joseph Antoci, MD Michael Flanagan, MD Scott Kantor, MD Paul Kraus, MD	Urology Specialists PC 160 Robbins Waterbury CT 06708

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

5650 Frank Maggiacomo, DO	Roger Ferland, MD	Silver Lake Medical Center 297 Pocasset Ave. Providence RI 02909
		Elmhurst Extended Care 50 Maude St. Providence RI 02908
		Cedar Crest Nursing Home 125 Scituate Ave. Cranston RI 02921
		Morgan Health Center 80 Morgan Ave. Johnston, RI 02919
5651 Barry McLean, MD	Sadri Avsar, MD Richard May, MD Frank McArthur, MD Michael Rosemore, DO William White, Pharmd	Southern Drug Research 1222 14th Ave. South Suites 101, 200, 205 Birmingham AL 35205
		Health South Medical Center Extended Care Facility 1201 11th Ave. South Birmingham AL 35205
		11009 Montgomery Higway Vestavia Hills AL 35216
		Lakeshore Rehabilitation Hospital 3800 Ridge Dr. Homewood AL 35209
5652 Michael Laplante, MD	Bernice Pynn, MD	3550 Cote-Des-Neiges Suite 550 Montreal Quebec H3H 1V4 Canada
		Montreal General Hospital 1650 Cedar Avenue Montreal Quebec H3G 1A5 Canada
		Clinical Research Consultant Group 3550 Cote-Des-Neiges Suite 550 Montreal Quebec H3H 1V4
5653 John Rubino, MD	Robert Bilbro, MD Gerald Blake, MD Lisa Dejarnette, MD William Dunlap, MD Allan Eure, MD Kenneth Leatherman, MD Mark McClure, MD	Raleigh Medical Group 3521 Haworth Dr. Raleigh NC 27609
		Capitol Urology 3901 Computer Dr. Raleigh NC 27609

		Central Carolina Urology Associates 3320 Wake Forrest Road Suite 100 Raleigh NC 27609
5654 Susan Rudberg, MD	Richard Moyer, MD Jon Rudberg, MD	Mesaba Clinic 1814 14th Ave. East Hibbing MN 55746
5657 Christopher Steidle, MD	John Brinkman, MD	Northeast Indiana Urology 7900 W. Jefferson Blvd. Suite 301 Fort Wayne IN 46804
5658 John Wegnke, MD	Percy Golson, PA Andrew Graf, MD Michael Kuglitsch, MD John Mahler, MD Gholam Malek, MD	Jackson Foundation/Physicians Plus 345 W. Washington Ave. Madison WI 537003 Physicians Plus Medical Grouup 20 S. Park St. Madison WI 53715
5661 Norman Zinner, MD	Alec Koo, MD Fredrick Wolk, MD	Doctors Urology Group Clinical Research Foundation 23441 Madison St. Suite 130 Torrance CA 90505 Western Clinical Research 23441 Madison St. Suite 130 Torrance CA 90505
5679 Lance Kirkegaard, MD	Shinobu Inoue Penny Miller J.H. Winemiller, MD	Future Healthcare Research Center 6210 75th St. West Suite A-200 Tacoma WA 98467 St. Clare Hospital 11315 Bridgeport Way Southwest Tacoma WA 98467
5734 Marc Gittleman, MD	Mark Christ, MD Barbara Montford, MD Lawrence Winton, MD	South Florida Medical Research 12900 Northeast 17th Ave. Suite 301 North Miami, FL 33181 South Florida Medical Research 610 N. Flamingo Road Pembroke Pines FL 33028 South Florida Medical Research 7150 W. 20th Ave. Suite 610 Hialeah FL 33016

		South Florida Medical Research 3700 Washington St. Suite 204A Hollywood FL 33021
5735 William Moseley, MD	D. Howard Lowe, MD Marianne Rochester, MD	San Diego Uro-Research 1901 Fourth Ave. Suite 200 San Diego CA 92101
5736 Thomas Shown, MD	C. Jeff Beach, PA David Cook, MD D. Patrick Currie, MD Andrew Griffin, MD Oliver Hart III, MD Oliver Hart Jr., MD Frederick Howell, MD Minnie Mercer Charles Reid, MD Allston Stubbs, MD	Peidmont Research Associates 1901 S. Hawthorne Rd. Suite 306 Winston-Salem NC 27103 Lyndhurst Urological Associates 2932 Lyndhurst Ave. Winston-Salem, NC 27103 Maplewood Urological 1806 S. Hawthorne Rd. Winston-Salem, NC 27103
5737 Joel Kaufman, MD	William Maniatis, MD Jonathan Seidlin, MD Thomas Watts, MD	Aurora Urology PC 1421 S. Potomac St. Suite 120 Aurora CO 80012 Aurora Urology 730 Potomac St. Suite 124 Aurora CO 80011
5738 Jacob Rajfer, MD	Abraham Grinvald, MD	Harbor-University of California Los Angeles Medical Center 100 W. Carson St. Torrance CA 90502
5781 C. Gilberto Brito, MD	Luis Argueso, MD Robert Bailey, MD Larry Bans, MD William Bohnert, MD Eric Zeldman, MD	Urology Associates LTD 202 E. Earll Dr. #360 Phoenix AZ 85012
6096 Paul Brower, MD	Steven Rudy, MD J. Bradley Taylor, MD Jay Young, MD	South Coast Urological Medical Group 31862 Coast Highway Suite 302 South Laguna CA 92677 South Coast Urological Medical Group 23961 Calle De La Magdelena Suite 534 Laguna Hills CA 92653
6097 D. Russell Locke, MD	Mark Dersch, MD Ira Klimberg, MD	924 North Highway 27/441 Lady Lake FL 32159 Urology Center of Florida 3201 Southwest 34th St. Ocala FL 34474

Study 154 –118/Complicated UTI:

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
5014 Ira Klimberg, MD	Mark Dersch, MD D. Russell Locke, MD	The Urology Center of Florida Inc. 3201 Southwest 34th St. Ocala, FL 34474
5133 Dennis Mikolich, MD	Perry Garber, MD Jacques Susset, MD	Independent Research Nurses Inc. 400 Reservoir Ave. Providence, RI 02907
		Scandinavian Home Inc. 1811 Broad St. Cranston, RI 02905
		Morgan Health Center 80 Morgan Ave. Johnston, RI 02919
		Heritage Hills Nursing Center 80 Douglas Pike Smithfield, RI 02917
		Tockwotton Home 180 George M. Cohan Memorial Blvd. Providence, RI 02903
		Oak Hill Nursing Home 544 Pleasant St. Pawtucket, RI 02860
		100 Highland Ave., Suite 100 Providence, RI 02906
5143 Jimmy Durden, MD	Thomas Bianchi, MD Patrick Bianchi, MD F. Keith Bufford, Jr., MD Andrew Hughes, MD Michael Peaden, MD Melvin Russell, MD	Community Medical Arts Center 875 Friendship Rd. Tallassee, AL 36078
		Tallassee Family Care 115 Herren Hill Rd. Tallassee, AL 36078
5630 Ronald Castellanos, MD	James Borden, MD Paul Bretton, MD William Evans, MD Ronica Kluge, MD Sergio Mather, MD David Michle, PhD Jasper Rizzo, DO Mary Yankaskas, MD Stephen Zellner, MD	Southwest Florida Urologic Associates 12651 Whitehall Dr. Ft. Myers, FL 33907
		Clinical Physiology Associates Clinical Study Center 4110 Center Pointe Dr., Suite 219 Ft. Myers, FL 33916
		Gulfshore Obstetrics and Gynecology 12631 Whitehall Drive Ft. Myers, FL 33907
		Southwest Florida Urologic Associates 507 Del Prado Boulevard Cape Coral, FL 33990

		Internal Medicine Associates 2675 Winkler Ave., Suite 300 Ft. Myers, FL 33901
5636 Stuart Sarshik, MD		Grandview Medical Research Inc. 711 Lawn Ave., Bldg. 1
		Grandview Hospital 700 Lawn Ave. Sellersville, PA 18960
		Pennridge Urological Associates 670 Lawn Ave. Sellersville, PA 18960
5637 Alan Tice, MD	Philip Craven, MD Peter Marsh, MD David McEniry, MD Lawrence Schwartz, MD Catherine Treseler, MD	Infections Limited PS 1624 South I St. #402 Tacoma, WA 98405
		Bel Air Nursing Home 630 S. Pearl Tacoma, WA 98465
5646 Stephen Farkas, MD		Future Healthcare Research Center Clinical Resources Inc. 754 S. Cleveland Ave. #200 Mogodore, OH 44260
		Barberton Citizens Hospital 155 Fifth St. NE Barberton, OH 44203
5662 Donald Gleason, MD	Curtis Dunshee, MD Samuel Grabb, MD David Killion, MD James MacDonald, MD Robert Reilly, MD H. Thomas Sethney, MD Stanley Suffecool, MD	Urological Assoc.of Southern Arizona, PC 5300 E. Erickson, Suite 106 Tucson, AZ 85712
5663 Michael Kuglitsch, MD	Percy Golson, PA Andrew Graf, MD John Mahler, MD Gholam Malek, MD John Wegenke, MD	Jackson Foundation/Physicians Plus 20 S. Park St. Madison, WI 53715
		Physicians Plus Medical Group 345 W. Washington Ave. Madison, WI 53703
5666 John Tuttle, MD		Clinic for Male Wellness, Inc. 120 N. Eagle Creek Medical Plaza Suite 121 Lexington, KY 40509

5667 W. Lamar Weems, MD	John Aldridge, MD W. Meredith Bradford, MD Thomas Fenter, MD James Keeton, MD Wafford Merrell, MD Robert Myers, MD Joe Ross, MD Charles Scruggs, MD Charles Secrest, MD	Mississippi Urology Clinic 1421 N. State St., Suite 403 Jackson, MS 39202 971 Lakeland Dr., Suite 657 Jackson, MS 39216
5668 W. Glen Wells, MD	Scott Kelly, MD Simon Mirelman, MD	Alabama Urology Assoc., PC 2022 Brookwood Medical Center Brookwood Acc., Suite 305 Birmingham, AL 35209 Childersburg Medical Surgical Center 34011 Highway 280 East Childersburg, AL 35044
5669 Jay Young, MD	Paul Brower, MD Steven Rudy, MD J. Bradley Taylor, MD	South Coast Urological Medical Group 23961 Calle De La Magdelena, Suite 534 Laguna Hills, CA 92653 South Coast Urological Medical Group 31862 Coast Highway, Suite 302 South Laguna, CA 92677
5681 Abdollah Iravani, MD	John Langton, MD	Central Florida Medical Research Center 1720 S. Orange Ave., Suite 401 Orlando, FL 32806 University of Central Florida UCF Student Health Services 400 Central Florida Blvd., Bldg. 27 Orlando, FL 32816 West Orange Manor 122 E. Division St. Winter Garden, FL 34777 Orlando Health Care Center 2000 N. Semoran Blvd. Orlando, FL 32807

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