CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-537/S038
19-847/S024
19-857/S027
19-858/S021
20-780/S008

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:   NDAs 19-537/S-038, 19-847/S-024, 19 957/S-027,
                       19-858/S-021, 20-780/S-008

Name of Drug: CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO®
                       (ciprofloxacin) IV Solution

Applicant: Bayer Corporation

Indications: Anthrax (post exposure prophylaxis)

Statistical Reviewer: Karen M. Higgins, ScD, HFD-725

Medical Reviewer: Andrea Meyerhoff, MD, HFD-590

Project Managers: Valerie Jensen and Leo Chan, HFD-590

I. INTRODUCTION

On March 1, 2000, Bayer Corporation submitted a supplemental NDA for ciprofloxacin for the indication of post exposure prophylaxis of inhalational anthrax. This application was submitted in response to an expressed public health need in the event of the intentional use of this biological agent. Inhalational anthrax was one of the six biological agents considered of greatest concern by the Centers for Disease Control and Prevention in 1999. The mortality rate of inhalational anthrax is as high as 80-100%. It is believed that in order for treatment to be effective it must begin soon after exposure, before signs of the disease emerge. There is little human experience with inhalational anthrax due to the fact that as a naturally occurring disease inhalational anthrax is extremely rare. There have been only approximately 20 cases in the United States in the past 100 years (Inglesby TV, Henderson DA, Bartlett JG et al. Anthrax as a biological weapon, medical and public health management. JAMA 281:1735-1745, 1999). For these two reasons, the rarity of disease and the extremely high mortality rate, a clinical study is not feasible.

An animal study was conducted in 1990 [   ] to assess the effects of three antibiotics and post exposure vaccine on inhalation anthrax in macaque monkeys (Friedlander AM, Welkos SL, Pitt MLM, et al. Postexposure prophylaxis against experimental inhalation anthrax. J Infect Dis 167:1239-1242, 1993). One of the three antibiotics studied was ciprofloxacin, which was found to have a significantly higher rate of survival over control. This non-human primate study will make up the primary efficacy information for this submission. Supportive information of drug exposure and *in vitro* data were also included in this submission. Please see the Clinical Pharmacology and Biopharmaceutics, Medical Officer's, and Microbiology reviews for a discussion of this information.

The safety information for this application relies of the large safety database and on the well-characterized safety profile of ciprofloxacin. Cipro was originally approved in 1987 and is approved for a wide range of indications. The use of ciprofloxacin in the United States exceeds [   ] prescriptions. The approved dose for ciprofloxacin ranges from 100-750 mg q 12 hour for adults. Proposed doses for this indication are oral 500 mg q12 h for 60 days and IV 400 mg q12 h for adults and 10 -15 mg/kg q12h for 60 days oral and IV for pediatrics. Information regarding its use in pediatrics as well-as its long-term, use greater than 30 days, have also been included in this submission (Segev S, Yaniv I, Haverstock D, Reinhart H. Safety of long-term therapy with ciprofloxacin: Analysis of controlled clinical trials and review. Clin Infect Dis 28:299-308, 1999 and Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use-safety report. Pediatr Infect Dis J 16:127-129, 1997). Please see the Medical Officer's review for a more complete discussion of safety.

Section two contains the primary efficacy information of post exposure prophylaxis of inhalational anthrax which consists of one study in monkeys. Section three contains conclusions. Please see the Medical Officer's report for the discussion of safety of ciprofloxacin along with a justification of the macaque model as a reasonable substitute for human data. Note that the sponsor has relied entirely on published literature.

II. EFFICACY

As stated above, the primary efficacy information on ciprofloxacin for prophylaxis of post exposure of inhalational anthrax is from a study conducted [   ] in 1990. This trial contained 60 monkeys that were randomized to one of 6 treatment arms with 10 monkeys per arm. Each monkey was exposed to approximately 12 LD50 (lethal dose sufficient to-kill 50% of those exposed to it) of inhalational anthrax. Treatment was started within 1 day after exposure. The 6 treatment groups were:
1. Control (saline)
2. Vaccine (0.5 mL of human anthrax vaccine)
3. Penicillin (procaine penicillin G, 180,000 units)
4. Ciprofloxacin (125 mg)
5. Doxycycline (30 mg)
6. Doxycycline plus Vaccine.

Both the control arm and the penicillin arm were given intramuscularly every 12 hours. The other antibiotics (ciprofloxacin and doxyclycline) were given by orogastic tube every 12 hours. As a control, the vaccine alone group received water by orogastic tube. The vaccine, given in groups 2 and 6, was given on days 1 and 15 post exposure. Groups 2, 4, 5, and 6 were anesthetized with tiletamine/zolazepam so medication/water could be given by orogastic tube.

Reviewers comment: The control arm (group 1) is most relevant for the penicillin comparison, because both groups received treatment intramuscularly and were not anesthetized or given treatment through orogastic tube. However, because it is unlikely that these differences greatly affected the outcome, it will be considered a control arm for the ciprofloxacin group as well.

The monkeys were treated with control or antibiotic for 30 days post exposure. They were then followed until death or until day 90. Note that the surviving monkeys were re-challenged with a second dose of anthrax between days 130 and 140 post initial

exposure. The results of this re-challenge are discussed in the reference but will not be discussed in this review.

Figure 1 is a graph of the survival curves for the 6 groups of monkeys. The first vertical line indicates when the control or antibiotic was stopped (day 30). The second vertical line indicates the study's primary analysis 'test of cure' day (day 90). There are two shapes of survival curves included in this figure. The control and the vaccine curves have very steep slopes very early on in the study. Both of these groups contained many early anthrax deaths. The other shape of curves is much more flat. All these curves are for treatments that contain one of the three antibiotic treatments.

There were 3 deaths that were determined to be unrelated to anthrax. The first was a monkey in the ciprofloxacin arm that died on day 5 after exposure from aspiration pneumonia due to problems with the orogastic tube when administering the drug. The second animal in the doxycycline plus vaccine group died 6 days after discontinuing doxycycline with no evidence of anthrax on autopsy. The third animal in the ciprofloxacin arm died 73 days after antibiotic treatment. This death was not thought to be anthrax related. Notice from the survival curves that all animals that died of anthrax on the antibiotic arms died after treatment and prior to day 60.

The following table contains an evaluable population analysis. This analysis includes only deaths due to anthrax, excludes animals who died early in the study, and looks at the death rate at Day 90. The p-value comparing the death rate of ciprofloxacin to that of control is highly significant (p=0.0011) showing that treatment with ciprofloxacin significantly reduces the rate of death due to anthrax over control in the macaque monkey model.

Evaluable Population Analysis: cause of death proven to be due to Anthrax

Treatment	Anthrax deaths	P vs. control[‡]	95%[1] CI of treatment – control
Control untreated	9/10		
Vaccine alone	8/10	> 0.1	(-54.1%, 37.2%)
Penicillin	3/10	0.0198	(-88.7%, -12.3%)
Ciprofloxacin	1/9*	0.0011	(-97.5%, -35.0%)
Doxycycline	1/10	0.0011	(-97.6%, -36.2%)
Doxycycline + vaccine	0/9[†]	0.0001	(-99.8%, -51.6%)

*One animal died 5 days after exposure from aspiration pneumonia, had no evidence of anthrax at autopsy, and was excluded from this analysis. Another animal died 73 days after antibiotic treatment. This death was not thought to be anthrax related and was not included in this analysis.

[†]One animal died 6 days after discontinuing doxycycline with no evidence of anthrax on autopsy. Cause of death remains unknown: the animal was excluded from this statistical analysis.

[‡] P-value was calculated using a two-tailed Fisher's exact test.

[1] 95% confidence interval was calculated using an exact method.

Reviewer's comment: Since multiple comparisons versus control were conducted initially for this study, an adjustment for multiple comparisons could be argued. Even with a conservative Bonferonni adjustment (alpha = 0.05/5 = 0.01), the ciprofloxacin arm is still significantly different than control.

The following table contains an intent to treat analysis. This analysis includes all deaths up to the re-challenge event (not discussed in this review). These results are supportive of the evaluable population analysis.

3

Treatment	All deaths	P vs. control[‡]	95%[1] CI of treatment - control
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[‡] P-value was calculated using a two-tailed Fisher's exact test.
[1] 95% confidence interval was calculated using an exact method.

Figure 1: Survival curves
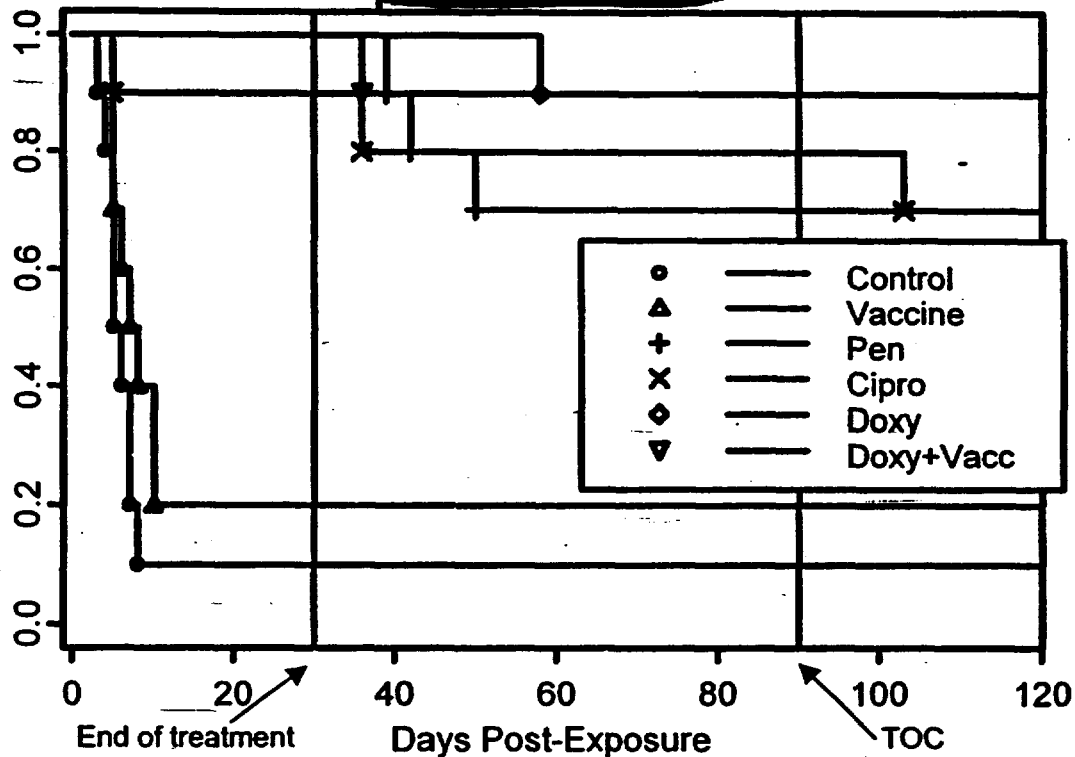
The actual dose of inhalational anthrax received varied from animal to animal. The doses ranged from 3 LD50 to 30 LD50, with an overall mean of 11.9 and standard deviation of 5.1. The doxycycline plus vaccine group had the highest mean dose of 14.6 LD50 and the ciprofloxacin group had the smallest mean dose of 9.6 LD50. Note that there was not a significant difference in mean doses across the 6 groups (p=0.1926). The control group had a mean of 12.6 LD50. Mean doses of ciprofloxacin versus control were not significantly different, however, the study was not powered to detect this difference.

In order to determine if the dose of inhalational anthrax lead to greater risk of death, the mean dose of those who died versus those who survived were compared for the group of monkeys receiving antibiotics and for the group that did not. For the 38 monkeys in

4

the antibiotic treatment groups, excluding 2 monkeys who died early of non-anthrax causes, the mean dose of anthrax of the survivors was 11.9 LD50 (n=33) while the mean dose of those who died of anthrax was 12.8 LD50 (n=5). In the placebo and vaccine groups, the monkeys who died had a mean LD50 of 11.8 (n=17) while those who survived had a mean LD50 of 12.0 (n=3). Neither analysis lead to a statistically significant difference.

Reviewer's comment: The study was not powered to determine if there was a significant difference in dose across treatment groups or if higher doses lead to higher rates of death. Cipro did have a lower mean LD50 than the other treatment groups, however, we could not determine if increased dose necessarily lead to increased mortality either in the antibiotic treated groups or in the control and vaccine alone groups.

III. CONCLUSIONS

In this unique situation of a rare disease with extremely high mortality rate, the threat of its use in a bioterrorism/biowarfare event, and with supportive *in vitro* and pharmacokinetic information, the macaque model is a reasonable substitute for human data. Given this information, ciprofloxacin has been shown to be effective for the use as post exposure prophylaxis for inhalational anthrax. The ciprofloxacin treated group had a significantly higher survival rate than the control group.

RECOMMENDED REGULATORY ACTION:

From a statistical perspective, the data provided by the sponsor support the approval of ciprofloxacin for the indication of post exposure prophylaxis of inhalational anthrax.

/S/   8/16/00

Karen M. Higgins, ScD
Statistical Team Leader, DB III

/S/
                    8/16/00

Concur: Aloka Chakravarty, PhD
                       Deputy Division Director, DB III

cc:
Orig. NDA 19-537, 19-847, 19-857, 19-858, 20-780
HFD-590
HFD-590/Dr. Albrecht
HFD-590/Dr. Roca
HFD-590/Dr. Meyerhoff
HFD-590/Ms. Jensen
HFD-590/Mr. Chan
HFD-725/Dr. Huque
HFD-725/Dr. Higgins
HFD-725/Ms. Robinette
This review contains 5 pages.

5