CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

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NDA:	50-747
Drug Name:	Synercid®(quinupristin/dalfopristin) I.V.
Applicant:	Rhône-Poulenc Rorer Pharmaceuticals, Inc.
Indications:	Infections due to Vancomycin-resistant *Enterococcus faecium* (VREF) and infections caused by *Staphylococcus aureus*
Documents Reviewed:	CANDA, dated September 10, 1997. Electronic data submitted on September 8, 1997
Medical Officer:	Alexander Rakowsky, M.D., HFD-520

1. Introduction

NDA 50-747 for Synercid® (quinupristin/dalfopristin) I.V. was submitted as a New Drug Application for infections due to Vancomycin-resistant *Enterococcus faecium* (VREF), including cases associated with concurrent bacteremia and infections caused by *Staphylococcus aureus* (including [redacted] susceptible and [redacted] resistant strains), in patients failing other therapies, including cases associated with concurrent bacteremia.

The submitted NDA composed of four non-comparative phase III studies, Studies 301, 398, 398B and Program 399. The primary effort of review will be given to studies 301 and 398 because these are two prospective studies and relatively well documented. Study 398B is the continuation of study 398. However, only very few patients were categorized by the Medical Officer as evaluable. Data of Study 399 were collected retrospectively and did not have a uniformed case report form. The more detailed information of studies 398B and 399 can be found in the Medical Officer's review. The indication of infections due to methicillin-resistant *Staphylococcus aureus* will not be mentioned in this review because the total number of cases across studies are very small. The Medical Officer will summarize the results in his review.

The review of this NDA will be organized by study. The design and results of each study will be summarized in the review, followed by the reviewer's discussion and conclusions. Finally, the overall assessment will be presented.

2. Infections due to Vancomycin-resistant *Enterococcus faecium* (Study 301 and Study 398)

2.1 Study 301

2.1.1 Summary of Design

Title of Study 301: Study of the Treatment of Infections due to Vancomycin-resistant *Enterococcus Faecium* (V.R.E.F.) with Synercid®

Study 301 was an open label, non-comparative study of the treatment with Synercid ® (quinupristin/dalfopristin) of patients suffering from infections caused by vancomycin-resistant *Enterococcus faecium* (VREF) . VREF was defined as *Enterococcus faecium* which had been shown to have a vancomycin sensitivity of intermediate or resistant via one of the following two criteria: 1. Disk Diffusion zone size of 16mm or less; 2. MIC of 8 or higher. The study, conducted in 44 centers in the United States, aimed at investigating Synercid safety and efficacy in patients infected with VREF who did not have any other therapeutic option. The following infections were considered under the protocol: intra-abdominal infection, skin and skin-structure infection, urinary tract infection, central catheter-related bacteremia, endocarditis and "other".

Patients enrolled in the study must be at least 18 years of age with one or more above documented infections. The use of Synercid® was indicated when the infection caused by VREF with resistant or intermediate *in vitro* susceptibility to all available clinically appropriate antibiotics or when patients had a documented intolerance to all available clinically appropriate antibiotics. Dose of Synercid® was recommended at 7.5 mg/kg, administered intravenously every 8 hours. The actual dose and treatment duration were to be decided by the investigators.

The protocol specified that clinical and bacteriological assessments were to be performed prior to treatment initiation, at treatment discontinuation, then at two follow-up visits: 5 to 10 days and approximately 30 days post-treatment discontinuation (an additional late follow-up visit was to apply to endocarditis patients). Patient Bacteriologic, Clinical and Overall Responses were to be assessed at the early follow-up visit(5 to 10 days post-treatment) or at discontinuation if patient drops out of the study. In light of the clinical complexity of typical VREF infected patients, the bacteriologic response was considered as primary in assessing the efficacy of Synercid.

Comments: The Medical Officer evaluated the efficacy of Synercid based on patients who were both clinically and bacteriologically evaluable. The evaluability criteria used for each infection site differed from the applicant's in some areas and the reasons for the differences were explained in his review. The impact caused by such differences is analyzed in this review.

Sample size was not specified in the protocol and the incidence rate of spontaneous bacteriological eradication as a historical control compared to Synercid was not provided in the protocol.

2.1.2 Summary of Results

Study drug was shipped to a total of 48 investigative sites, of which 44 enrolled a total of 265 patients (Table 1). The sites were all located in the United States. All the 265 patients enrolled in the study (100%) received Synercid intravenously. The first patient was treated on 24 October 1994 and the last patient visit was on 22 February 1996. Eight of these patients, who had received a prior treatment course with Synercid for the same emergency-use indication in the current study, were excluded by the applicant from the All-treated Population. The Medical Officer considered these patients non-evaluable in his review. One patient(#04301) had two indications, urinary tract infection and central catheter related bacteremia. The applicant categorized this patient non-evaluable for both infections, but the Medical Officer considered him clinically evaluable and failed to treatment for both infections.

Table 1 Summary of Populations

Population	RPR Number (%) of Patients	FDA Number(%) of Patients
All Enrolled	265 (100.0)	265 (100.0)
Eight patients with prior synercid treatment	excluded	non-evaluable
Clinically Evaluable	139 (52.5)	116 (43.8)

Changes in clinical evaluability by the Medical Officer are shown in Table 2. Forty-two (15.8%) patients with Synercid are categorized as non-evaluable by the Medical Officer while the applicant considered them clinically evaluable. The number of patients changed from non-evaluable considered by the applicant into evaluable by the Medical Officer is 19 in the Synercid group.

Table 2.Consistency of Clinical Evaluability between FDA and the Sponsor

Study 301		
	FDA Evaluable	FDA Non-evaluable
Sponsor Evaluable	97 (36.6%)	42 (15.8%)
Sponsor Non-evaluable	19 (7.2%)	107 (40.4%)

Reasons for Non-evaluable

One hundred and seven patients with Synercid are considered not clinically evaluable by both the Medical Officer and the applicant. The reasons of non-evaluable for these patients categorized by the Medical Officer are listed in Table 3.

Table 3. Reasons for Agreed Non-evaluable By FDA and the Applicant in Study 301

Reasons For Non-evaluable*	Synercid N=107
Prohibited Antibiotic Prior to Study Drug	1
Prohibited Concomitant Treatment/Antibiotic	1
Missing Baseline Data	3
Insufficient Treatment Duration	21
Missing Required Efficacy data	21
Incorrect Diagnosis	11
Condition Precluding Evaluation of Response	35
Baseline Assessment Deviation	2
Efficacy Assessment Deviations	3
Infection Type	1
Previous Participation in Synercid Study	8

*Reasons for non-evaluable are given by the Medical Officer.

Forty-two patients in the Synercid group are changed from clinically evaluable as defined by the applicant into non-evaluable by the Medical Officer. The reasons for these changes are shown in Table 4.

Table 4. Reasons For Changes From Evaluable to Non-evaluable by the Medical Officer

Reasons For Non-evaluable	Synercid N=42
Prohibited Antibiotic	4
Missing Baseline Data	6
Insufficient Treatment Duration	1
Missing Required Efficacy data	14
Incorrect Diagnosis	8
Condition Precluding Evaluation of Response	8
Insufficient Number/Type & Sign/Symp at Baseline	1

There are another 19 patients who were changed from clinically non-evaluable as defined by the applicant to evaluable by the Medical Officer.

Efficacy

Clinically Evaluable patients accounted for 43.8% of whole population enrolled. The clinical outcomes of many patients in the non-evaluable population (49 patients) could not be determined even by the applicant due to conditions precluding evaluation of response, missing efficacy data or insufficient treatment duration. Table 5 presents the efficacy results of the FDA's and the applicant's.

Table 5. Summary of Efficacy Analysis

	FDA	Applicant
Study 301	N=116	N=139
Clinical cure or improvement	65(56%)	102(73%)

A summary of the number of patients by indication is presented in Table 6.

Table 6 Summary of Number of Patients by Indication

	Number (%) of Patients*	
	All Treated Patients	FDA's Evaluable population
Total	266 (100.0)	117 (100.0)
Intra-abdominal infection	89 (33.5)	46 (39.3)
Bacteremia of unknown source	71 (26.7)	17 (14.5)
Urinary tract infection	26 (9.8)	17 (14.5)
Skin and skin structure infection	25 (9.4)	10 (8.5)
Central catheter-related bacteremia	22 (8.3)	9 (7.7)
Other	10 (3.8)	3 (2.6)
Bone and joint infection	8 (3.0)	5 (4.3)
Respiratory tract infection	5 (1.9)	2 (1.7)
Deep wound other than abdominal	4 (1.5)	4 (3.4)
Intravascular site infection	3 (1.1)	3 (2.6)
Endocarditis	3 (1.1)	1 (0.9)

*Patients who were infected with multiple sites could be counted more than once..

A summary of both FDA's and the applicant's results about the number of patients cured or improved by indication are presented and compared in Table 7. The applicant's response rates per indication are higher than the FDA's. The reasons for this difference were due to the different evaluability and success criteria used in the analyses. Please refer to the Medical Officer's review for detailed discussion on these differences.

Table 7 Clinical Success Rates by Indication

	Number (%) of Patients cured or improved*			
	Applicant's Evaluable population		FDA's Evaluable population	
Total	102/139	(73%)	65/117	(56%)
Intra-abdominal infection	36/51	(71%)	23/46	(50%)
Bacteremia of unknown source	14/23	(61%)	9/17	(53%)
Urinary tract infection	15/18	(83%)	11/17	(65%)
Skin and skin structure infection	15/18	(83%)	7/10	(70%)
Central catheter-related bacteremia	8/10	(80%)	5/9	(56%)
Other	5/6	(83%)	3/3	(100%)
Bone and joint infection	3/4	(75%)	2/5	(40%)
Respiratory tract infection	2/2	(100%)	1/2	(50%)
Deep wound other than abdominal	3/3	(100%)	4/4	(100%)
Intravascular site infection	1/3	(33%)	0/3	(0%)
Endocarditis	0/1	(0%)	0/1	(0%)

* Patients who were infected with multiple sites could be counted more than once.

Impact of Changes made by the Medical Officer

Among those patients agreed by the Medical Officer and the applicant to be clinically evaluable (97 in the Synercid group), 11 of them were changed by the Medical Officer from cure to failure. The rest of clinical outcomes were agreed between the Medical Officer and the applicant.

Among those patients considered clinically evaluable by the applicant but not by the Medical Officer, 34 out of 42 were categorized as cure by the applicant.

In addition, 19 patients with Synercid were changed from non-evaluable to evaluable by the Medical Officer. Among them, 11 patients treated with synercid were reclassified as failures by the Medical Officer and 8 patients were assessed to be cured by the Medical Officer.

Baseline Characteristics

Patients in each population (evaluable vs non-evaluable) were more likely to be aged <65 years than ≥65 years, male than female, and Caucasian than non-Caucasian. All patients were enrolled in the United States. The distribution of important underlying medical conditions such as APACHE score, bacteremia at entry, neutrophils count, was statistically significantly different between the evaluable population and non-evaluable population as shown in Table 8. Patients in the non-evaluable population were sicker than those in the evaluable population. As a result, more deaths were reported in the non-evaluable population than in the evaluable population (p-value<0.001).

Table 8.Comparison of Risk Factors in Evaluable Population and Non-evaluable population

	FDA's Evaluable	FDA's Non-evaluable	p-value**
Age less than 65	N=116 84 (71.8%)	N=140* 103 (73.6%)	0.751
Neutrophils < 500 Yes (%)	N=116 5 (4.3%)	N=141* 16 (11.4%)	0.039
APACHE at Entry (<10,11-20,>20)	N=115* (53,52,10)	N=137* (40,61,36)	0.001
Bacteremia at Entry Yes (%)	N=116 17 (14.5%)	N=149 54 (36.2%)	0.001
Death on the study Yes(%)	N=116 30(25.9%)	N=149 98(65.8%)	<0.001

* N indicates the total number of patients used in the calculation. Patients with missing data are excluded.
** p value is calculated based on Mantel-Haenszel test.

Safety

An overview of safety results is presented in Table 9.

Table 9. Safety Summary

Safety Parameter	**Number (%) Patients N = 265**
Adverse non-venous events	263 (99.2)
Adverse venous events in patients with peripheral catheter administration	38/73 (52.1)
Adverse non-venous events related to study medication[a]	77 (29.1)
Most common (≥5%):	
Arthralgia	26 (9.8)
Myalgia	20 (7.5)
Body system	
Musculoskeletal system	30 (11.3)
Digestive system	19 (7.2)
Body as a whole	19 (7.2)
Skin & appendages	11 (4.2)
Cardiovascular system	6 (2.3)
Urogenital system	5 (1.9)
Metabolic & nutritional disorders	5 (1.9)
Hemic and lymphatic system	3 (1.1)
Nervous system	2 (0.8)
Respiratory system	2 (0.8)
Deaths	128 (48.3)
Other serious adverse clinical events[b]	118 (44.5)
Treatment discontinuation due to adverse clinical events[b]	83 (31.3)
Treatment discontinuation due to adverse laboratory event	2 (0.8)

[a] Probable or possible relationship
[b] Includes venous and non-venous events
Data Source: Section 12, Tables 12.6.1, 12.6.10, 12.6.12, 12.6.13, 12.6.20, 12.6.21, 12.6.22

All 265 enrolled patients were included in the safety analysis. Interpretation of clinical safety results is rendered difficult by the open, noncomparative design of the study and the high frequency of severe underlying medical conditions. The overall mortality rate in study patients was 48.3%. One hundred eleven (44.5%) of patients had serious adverse clinical events other than death. Eighty five patients (32.1%) patients discontinued treatment due to adverse events.

The frequency of reported adverse clinical events was similar by age, gender, and race. Thirty-eight of 73 (52.1%) patients who received Synercid through a peripheral venous catheter had an adverse venous event. The adverse non-venous clinical events of note, in part because of their stated possible or probable relationship to treatment, included nausea, arthralgias and myalgias. Nausea was reported in 50 (18.9%) patients, of which 10 events were possibly or probably related to treatment. Arthralgias occurred in 44 (16.6%) patients (26 possibly or probably related); myalgias occurred in 33 (12.5%) patients; 20 events were considered possibly or probably related. Arthralgias and myalgias accounted for 3.4% and 3.0% of treatment discontinuations, respectively. The etiology of these arthralgias and myalgias is unknown.

As with clinical safety variables, interpretation of changes in laboratory parameters is difficult due to the high degree of illness of these patients and the lack of a comparator group. In addition, comparison of on-treatment changes with post-treatment changes may not be justified since patients surviving to have post-treatment values recorded may have been less ill than patients whose only observations were on-treatment before their demise. Laboratory trends were examined to determine whether there was an equal tendency for an increase and decrease in laboratory values on treatment. Of note, a greater percentage of Synercid patients experienced an increase versus a decrease in AST, total bilirubin, conjugated bilirubin, alkaline phosphatase, and creatinine. Similarly, a greater percentage of Synercid patients experienced an increase versus a decrease in white blood cells and a decrease versus an increase in hemoglobin. At post-treatment visits, the magnitude of these discordances decreased, but the significance of this observation is unknown because the numbers of patients evaluated were substantially smaller than on-treatment, likely reflecting drop-out of the most severely ill patients.

2.1.3 Discussion and Conclusions

Clinical Evaluability Rate

The clinical evaluability rates were relatively low, 43.8%, in this study. Most of non-evaluable patients were due to conditions precluding evaluation of response, insufficient efficacy data or insufficient treatment duration. In addition, 49 (19%) out of all patients treated with synercid did not have a definitive clinical outcome assigned by the applicant. The applicant called these patients with "indeterminate" clinical responses. As a result, a meaningful intent-to-treat analysis is not feasible. The treatment effect must heavily rely upon the evaluable population. A potential selection bias of evaluable patients might occur. To assess the similarities of evaluable and non-evaluable populations, comparisons of demographic characteristics and risk factors between the two populations were performed. Statistically significant differences in APACHE score, bacteremia at baseline, neutropenic at baseline were noticed. Patients in the non-evaluable population were more severely ill than those in evaluable population. More deaths were reported in the non-evaluable population. As the differences between the evaluable and non-evaluable populations were noticed, the evaluable population may not fully reflect the total population enrolled in the study. The response rate from the evaluable population might be over-estimated for the population based on the inclusion/exclusion criteria.

Efficacy

Among the evaluable population, the clinical success rate of synercid is 56%. There is no control group, concurrent or historical, to be compared with Synercid. A large part of patients were excluded from the estimation of success rate. The success rate in the evaluable patients is not as high as to such a level which could overweight the deficiencies in the study. Therefore, the result of this trial needs to be confirmed by a well-controlled clinical study.

Safety

Interpretation of clinical safety results is rendered difficult by the open, noncomparative design of the study and the high frequency of severe underlying medical conditions. Over 99% of patients experienced at least one adverse non-venous event. Seventy seven (29%) of patients had adverse non-venous experience which was considered related to Synercid by the investigator. In addition to the overall mortality rate in study patients (48.3%), the rate of other serious adverse events is 44.5% of all treated patients. Patients discontinued treatment due to adverse events accounts for 32% of total population.

2.2 Study 398

2.2.1 Summary of Design

Title of Study 398: Open Study of Synercid® (quinupristin/dalfopristin, RP 59500) for Emergency Use (Infections Due to Resistant Bacteria, Treatment Failure or in Treatment-Intolerant Patients)

Synercid was to be authorized for use within this Emergency Use Protocol for patients with infections due to pathogens presumed to be susceptible to Synercid where no alternative therapy exists which included the following:

- Infection with an organism resistant to all clinically appropriate antibiotics
- Intolerance to all available clinically appropriate antibiotics
- Documented treatment failure with all clinically appropriate antibiotics

The majority of the patients treated under this protocol were expected to be those with a vancomycin-resistant *Enterococcus faecium* (VREF) infection. Infections due to other organisms including staphylococci, streptococci, other enterococci and *Legionella sp.* would also be permitted in the study. The possibility of supplying Synercid on an emergency use basis to patients with infections caused by organisms other than those previously mentioned would be reviewed on a case by case basis.

Dose of Synercid® was recommended at 7.5 mg/kg, administered intravously every 8 hours, or every 12 hours. The actual dose and treatment duration were to be decided by the investigators.

Clinical and bacteriological assessments were to be performed prior to treatment initiation, at treatment discontinuation, then at follow-up visit (1 to 3 weeks post-treatment discontinuation). No analysis plan had been pre-specified in the protocol.

Comments: The evaluability criteria used for each infection site can be found in the Medical Officer's review. The reasons why they were different from the applicant's were explained in his review. The impact caused by such differences is analyzed in this review.

2.2.2 Summary of Results

All of the 219 patients enrolled in the study received Synercid intravenously, but data were available for 214 patients (97.7%). The following patients were excluded by the applicant from efficacy analyses because they previously had been enrolled in one of the emergency-use programs (Study 399 or the current study): 98510 (FR00870), 98037 (US01767), 98511 (GB00420) and 98385 (US01827). The Medical Officer considered them non-evaluable. Of 210 patients remaining, 6 patients had more than 2 infection sites simultaneously. The evaluability and clinical outcome for multiple infection sites turned out to be consistent by Medical Officer's assessment. The results are summarized in Table 10.

Table 10 Summary of Populations

Population	RPR Number (%) of Patients	FDA Number(%) of Patients
All Enrolled	219 (100.0)	219 (100.0)
Patients excluded	9 (5 w/o data, 4 prior synercid trt)	5 (without data)
Clinically Evaluable	83/210 (39.5)	70/214 (32.7)

Changes in clinical evaluability by the Medical Officer are shown in Table 11. Thirty patients with Synercid are categorized as non-evaluable by the Medical Officer while the applicant considered them clinically evaluable. The number of patients changed from non-evaluable considered by the applicant into evaluable by the Medical Officer is 18 in the Synercid group.

Table 11.Consistency of Clinical Evaluability between FDA and the Sponsor

Study 398 (N=214)		
	FDA Evaluable	FDA Non-evaluable
Sponsor Evaluable	52 (24%)	30 (14%)
Sponsor Non-evaluable	18 (9%)	114(53%)

Reasons for Non-evaluable

One hundred fourteen patients with Synercid are considered not clinically evaluable by both the Medical Officer and the applicant. The reasons of non-evaluable for these patients categorized by the Medical Officer are listed in Table 12.

Table 12. Reasons for Agreed Non-evaluable By FDA and the Applicant in Study 398

Reasons For Non-evaluable*	Synercid N=114
Prohibited Antibiotic Prior to Study Drug	4
Prohibited Antibiotic Post Study Drug	2
Prohibited Concomitant Treatment/Antibiotic	2
Missing Baseline Data	2
Insufficient Treatment Duration	19
Missing Required Efficacy data	8
Incorrect Diagnosis	28
Condition Precluding Evaluation of Response	40
Efficacy Assessment Deviations	1
Treatment Stop Other Than Failure	2
Previous Participation in Synercid Study	4
Insufficient Number/Type $ signs/Symps at Baseline	1
Poor Medication Compliance	1

*Reasons for non-evaluable are given by the Medical Officer.

Thirty patients in the Synercid group are changed from clinically evaluable into non-evaluable by the Medical Officer. The reasons for these changes are shown in Table 13.

Table 13. Reasons For Changes From Evaluable to Non-evaluable by the Medical Officer

Reasons For Non-evaluable	Synercid N=30
Prohibited Antibiotic	5
Missing Baseline Data	4
Missing Required Efficacy data	12
Incorrect Diagnosis	6
Condition Precluding Evaluation of Response	1
Missing Efficacy Visit	1
Previous Participate in Synercid Study	1

There are another 18 patients who were changed from clinically non-evaluable to evaluable by the Medical Officer.

Efficacy

Clinically Evaluable patients represented 33% of whole population enrolled. The clinical outcomes of many patients in the non-evaluable population (70 patients) could not be determined even by the applicant due to conditions precluding evaluation of response, missing efficacy data or insufficient treatment duration. Table 14 presents the efficacy results of the FDA's and the applicant's.

Table 14. Summary of Efficacy Analysis

	FDA	Applicant
Study 398	N=70	N=83
Clinical cure or improvement	32(46%)	67(81%)

A summary of the number of patients by indication is presented in Table 15.

Table 15 Summary of Number of Patients by Indication

	Number (%) of Patients*	
	All Treated Patients	FDA's Evaluable population
Total	216 (100)	71 (100)
Intra-abdominal infection	59 (27.3)	21 (29.6)
Bacteremia of unknown source	62 (28.7)	16 (22.5)
Urinary tract infection	12 (5.6)	6 (8.5)
Skin and skin structure infection	16 (7.4)	5 (7.0)
Central catheter-related bacteremia	20 (9.3)	6 (8.5)
Other	8 (3.7)	4 (5.6)
Bone and joint infection	20 (9.3)	8 (11.2)
Respiratory tract infection	5 (2.3)	1 (1.4)
Deep wound other than abdominal	0 (0.0)	0 (0.0)
Intravascular site infection	0 (0.0)	0 (0.0)
Endocarditis	14 (6.5)	4 (5.6)

*Patients who were infected with multiple sites could be counted more than once.

A summary of both FDA's and the applicant's results about the number of patients cured or improved by indication are presented and compared in Table 16. The applicant's response rates per indication are higher than the FDA's. The reasons for this difference were due to the different evaluability and success criteria used in the analyses. Please refer to the Medical Officer's review for detailed discussion of the differences.

Table 16 Clinical Success Rates by Indication

	Number (%) of Patients cured or improved*	
	Applicant's Evaluable population	FDA's Evaluable population
Total	67/83 (81%)	33/71 (46%)
Intra-abdominal infection	20/23 (87%)	8/21 (38%)
Bacteremia of unknown source	13/17 (76%)	3/16 (19%)
Urinary tract infection	7/7 (100%)	6/6 (100%)
Skin and skin structure infection	4/5 (80%)	3/5 (60%)
Central catheter-related bacteremia	7/7 (100%)	4/6 (67%)
Other	3/5 (60%)	2/4 (50%)
Bone and joint infection	10/12 (83%)	6/8 (75%)
Respiratory tract infection	1/2 (50%)	0/1 (0%)
Deep wound other than abdominal	0/0 —	0/0 —
Intravascular site infection	0/0 —	0/0 —
Endocarditis	2/5 (40%)	1/4 (25%)

* Patients who were infected with multiple sites could be counted more than once.

Impact of Changes made by the Medical Officer

Among those patients agreed by the Medical Officer and the applicant to be clinically evaluable (52 in the Synercid group), 6 of them were changed by the Medical Officer from cure to failure. The rest of clinical outcomes were agreed between the Medical Officer and the applicant.

Among those patients considered clinically evaluable by the applicant but not by the Medical Officer, 28 out of 30 were categorized as cure by the applicant.

In addition, 18 patients with Synercid were changed from non-evaluable to evaluable by the Medical Officer. All of them were reclassified as failures by the Medical Officer.

Baseline Characteristics

Patients in each population (evaluable vs non-evaluable) were more likely to be aged <65 years than ≥65 years, male than female, and Caucasian than non-Caucasian. Most of patients were enrolled in the United States. The distribution of important underlying medical conditions such as bacteremia at entry, neutrophils count, immunodepression, HIV infection, was comparable between the evaluable population and non-evaluable population as shown in Table 17. However, patients in the evaluable population were treated longer with synercid than those in the non-evaluable population (p=0.018). More deaths were reported in the non-evaluable population than in the evaluable population (p=0.009).

Table 17.Comparison of Risk Factors in Evaluable Population and Non-evaluable population

	FDA's Evaluable	FDA's Non-evaluable	p_value (Mantel-Haenszel test)
Age less than 65	N=70 56 (80.0%)	N=140* 86 (61.4%)	0.007
Neutrophils < 500 Yes (%)	N=70 6 (8.6%)	N=140* 10 (7.1%)	0.714
Bacteremia at Entry Yes (%)	N=70 16 (22.9%)	N=144 48 (33.3%)	0.128
Death Yes(%)	N=70 25(36%)	N=144 79(55%)	0.009
Duration of treatment median days	17	11	0.018**

* N indicates the number of patients with data. Patients with missing data were excluded from the analysis.
** T-test.

Safety

An overview of safety results is presented in Table 18. In this emergency-use study, serious adverse clinical events and any other adverse events which the investigator determined could be related to Synercid were to be recorded on the case report form.

Table 18. Safety Summary

Safety Parameter	Number (%) Patients N = 214
Adverse non-venous events	147 (68.7)
Adverse venous events in patients with peripheral catheter administration	17/44 (38.6)
Adverse non-venous events related to study medication[a]	
Most common (≥5%):	39 (18.2)
Arthralgia	
Related adverse events by body system	17 (7.9)
Musculoskeletal system	
Digestive system	19 (8.9)
Body as a whole	8 (3.7)
Skin & appendages	5 (2.3)
Nervous system	5 (2.3)
Urogenital system	3 (1.4)
Hemic & lymphatic system	2 (0.9)
Cardiovascular system	2 (0.9)
Metabolic & nutritional disorders	1 (0.5)
Deaths	1 (0.5)
Other serious adverse clinical events[b]	104 (48.6)
Treatment discontinuation due to adverse clinical events[b]	33(15.4)
Treatment discontinuation due to adverse laboratory events	80 (37.4)
	6 (2.8)

[a] For each patient, only the maximum relationship (possible or probable) recorded for the same adverse event is taken into account into the calculations. For the total number of patients with adverse events and for each body system, patients having one or more adverse event are counted only once.

[b] Includes venous and non-venous events

Data Source: Section 12, Tables 12.6.1, 12.6.10, 12.6.12, 12.6.13, 12.6.14, 12.6.18, 12.6.20, 12.6.22

A summary of the most frequently reported adverse non-venous events (occurring in at least 5% of patients) is presented in Table 19.

Table 19. Summary of Most Frequently Reported (At Least 5% of Patients) Adverse Non-venous Events

Body system Adverse event (COSTART term)	Number (%) Patients[a] N = 214
Patients without adverse events	**67 (31.3)**
Patients with at least one adverse event	**147 (68.7)**
Body as a whole	**91 (42.5)**
Sepsis	54 (25.2)
Aggravation reaction[b]	28 (13.1)
Cardiovascular system	**55 (25.7)**
Heart arrest	16 (7.5)
Hypotension	15 (7.0)
Respiratory system	**42 (19.6)**
Apnea	25 (11.7)
Digestive system	**33 (15.4)**
Musculoskeletal system	**22 (10.3)**
Arthralgia	19 (8.9)
Hemic & lymphatic system	**22 (10.3)**
Urogenital system	**16 (7.5)**
Skin & appendages	**11 (5.1)**
Nervous system	**9 (4.2)**
Metabolic & nutritional disorders	**7 (3.3)**

[a] Although a patient may have had two or more adverse events in a body system category, the patient was only counted once in the body system total. For this reason, the separate adverse event totals may not sum to the body system total. A similar remark applies for the body system totals and the number of patients with any adverse events. If an individual adverse event was reported by the same patient more than once, the adverse event was counted only once. This applies to subsequent adverse event tables of the same kind.

[b] Worsening of an underlying condition

Data Source: Section 12, Table 12.6.1

Overall, the greatest frequency of events occurred in the body as a whole system. The most prevalent events in this system were sepsis and aggravation reaction (worsening of an underlying condition).

A summary of the most frequently reported (occurring in at least 2% of patients) related (possible or probable) adverse non-venous events is presented in Table 20.

Table 20. Summary of Most Frequently Reported (At Least 2% of Patients) Related Adverse Non-venous Events

Body system Adverse event	Number (%) Patients[a] N = 214
Patients with related adverse events	39 (18.2)
Body as a whole	**5 (2.3)**
Cardiovascular system	**1 (0.5)**
Digestive system	**8 (3.7)**
Nausea	6 (2.8)
Hemic and lymphatic system	**2 (0.9)**
Metabolic & Nutritional Disorders	**1 (0.5)**
Musculoskeletal system	**19 (8.9)**
Arthralgia	17 (7.9)
Myalgia	9 (4.2)
Nervous system	**3 (1.4)**
Skin & appendages	**5 (2.3)**
Urogenital system	**2 (0.9)**

[a] Each patient experiencing an adverse non-venous event is counted only once in this table. The adverse event with the highest relationship was used to complete the cell total.

Data Source: Section 12, Table 12.6.10

Thirty-nine (18.2%) patients enrolled in the study reported an adverse non-venous event considered to be related to study medication. Overall, the most common adverse non-venous event related to study medication was arthralgia, which was the only adverse non-venous event that occurred in more that 5% of patients.

A summary of the most frequently reported (occurring in at least 2% of patients) severe adverse non-venous events is presented in Table 21.

Table 21. Summary of Most Frequently Reported (At Least 2% of Patients) Severe Adverse Non-venous Events

Body system Adverse event	Number (%) Patients[a] N = 214
Patients with severe adverse events	120 (56.1)
Body as a whole	
Sepsis	**81 (37.9)**
Aggravation reaction[b]	52 (24.3)
Immune system disorder	28 (13.1)
Peritonitis	5 (2.3)
	5 (2.3)
Cardiovascular system	
Heart arrest	**48 (22.4)**
Hypotension	16 (7.5)
Heart failure	14 (6.5)
	9 (4.2)
Respiratory system	
Apnea	**40 (18.7)**
Pneumonia	24 (11.2)
Respiratory distress syndrome	9 (4.2)
	5 (2.3)
Digestive system	
Gastrointestinal hemorrhage	**25 (11.7)**
Hepatic failure	10 (4.7)
	7 (3.3)
Hemic and lymphatic system	
Acute myeloblastic leukemia	**20 (9.3)**
Pancytopenia	4 (1.9)
	4 (1.9)
Urogenital system	
Kidney failure	**11 (5.1)**
	8 (3.7)
Musculoskeletal system	
Arthralgia	**8 (3.7)**
Myalgia	7 (3.3)
	5 (2.3)
Metabolic & nutritional disorders	**6 (2.8)**
Nervous system	**3 (1.4)**

[a] Each patient experiencing an adverse non-venous event is counted only once in this table. The adverse event with the highest severity was used to complete the cell total.

[b] Worsening of an underlying condition

Data Source: Section 12, Table 12.6.11

Approximately half of enrolled patients experienced a severe adverse non-venous event. The two most prevalent severe adverse non-venous events, sepsis and aggravation reaction (worsening of an underlying condition), occurred in the body as a whole system.

2.2.3 Discussion and Conclusions

Clinical Evaluability Rate

The clinical evaluability rates were relatively low, 32.7%, in this study. Most of non-evaluable patients were due to conditions precluding evaluation of response, violation of inclusion criteria, insufficient efficacy data or insufficient treatment duration. In addition, 70 (33%) out of all patients treated with synercid did not have a definitive clinical outcome assigned by the applicant. The applicant called these patients with "indeterminate" clinical responses. As a result, a meaningful intent-to-treat analysis is not feasible. The treatment effect must heavily rely upon the evaluable population. A potential selection bias of evaluable patients might occur. To assess the similarities of the evaluable and non-evaluable populations, comparisons of demographic characteristics and risk factors between the two population were performed. No statistically significant differences were noticed for the most of risk factors under consideration. However, more deaths were reported in the non-evaluable population. More patients less than 65 years old were observed in the evaluable population. The treatment duration was longer in the evaluable patients than in the non-evaluable patients. The differences between the evaluable and non-evaluable populations were less noticeable compared to study 301. The response rate from the evaluable population is also lower (46%) in Study 398 compared to 56% in Study 301.

Efficacy

Among the evaluable population, the clinical success rate of synercid is 46%. There is no control group, concurrent or historical, to be compared with synercid. A large part of patients were excluded from the estimation of success rate. The success rate in the evaluable patients is not as high as to such a level which could overweight the deficiencies in the study. Therefore, the result of this trial needs to be confirmed by a well-controlled clinical study.

Safety

Interpretation of clinical safety results is rendered difficult by the open, noncomparative design of the study and the high frequency of severe underlying medical conditions. Around 69% of patients experienced at least one adverse non-venous event. Thirty nine (18.2%) of patients had adverse non-venous experience which was considered related to Synercid by the investigator. In addition to the overall mortality rate in study patients (48.6%), the rate of other serious adverse events is 15.45% of all treated patients. Patients discontinued treatment due to adverse events takes 40% of total population.

3. Statistical Reviewer's Overall Assessment

Both studies 301 and 398 showed relatively low evaluability rates in total population and moderate successful rates in the evaluable population. The mortality rates in both studies are also approximately 50%. Patients discontinued the treatment in two studies account for 30% to 40% of all patients treated. In addition, both studies lack of a control group, concurrent or historical, for comparison.

Study 398B provides less valuable information than study 301 and study 398 because only very few patients were categorized by the Medical Officer as evaluable. Data of Study 399 were collected retrospectively and did not have a uniformed case report form.

As a summary of this review, Synercid is relatively safe to treat patients who are infected by Vancomycin-resistant *Enterococcus faecium*. The efficacy of Synercid for this indication needs to be confirmed by an adequate, well-controlled clinical study.

/S/

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Archival:NDA #50-747
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HFD-725/Dr. Shen
HFD-725/Dr. Huque
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Chron.

Statistical Review and Evaluation

JUN 1 1998

NDA: 50-748
Drug Name: Synercid®(quinupristin/dalfopristin) I.V.
Applicant: Rhône-Poulenc Rorer Pharmaceuticals, Inc.
Indications: (1) Complicated skin and skin structure infections;

[redacted]

Documents Reviewed: CANDA, dated September 10, 1997. Electronic data submitted on September 8, 1997
Medical Officer: Susan Thompson, M.D. and Alexander Rakowsky, M.D., HFD-520

[redacted]

1. Introduction

NDA 50-748 for Synercid® (quinupristin/dalfopristin) I.V. was submitted as a New Drug Application with three indications. These three indications are:

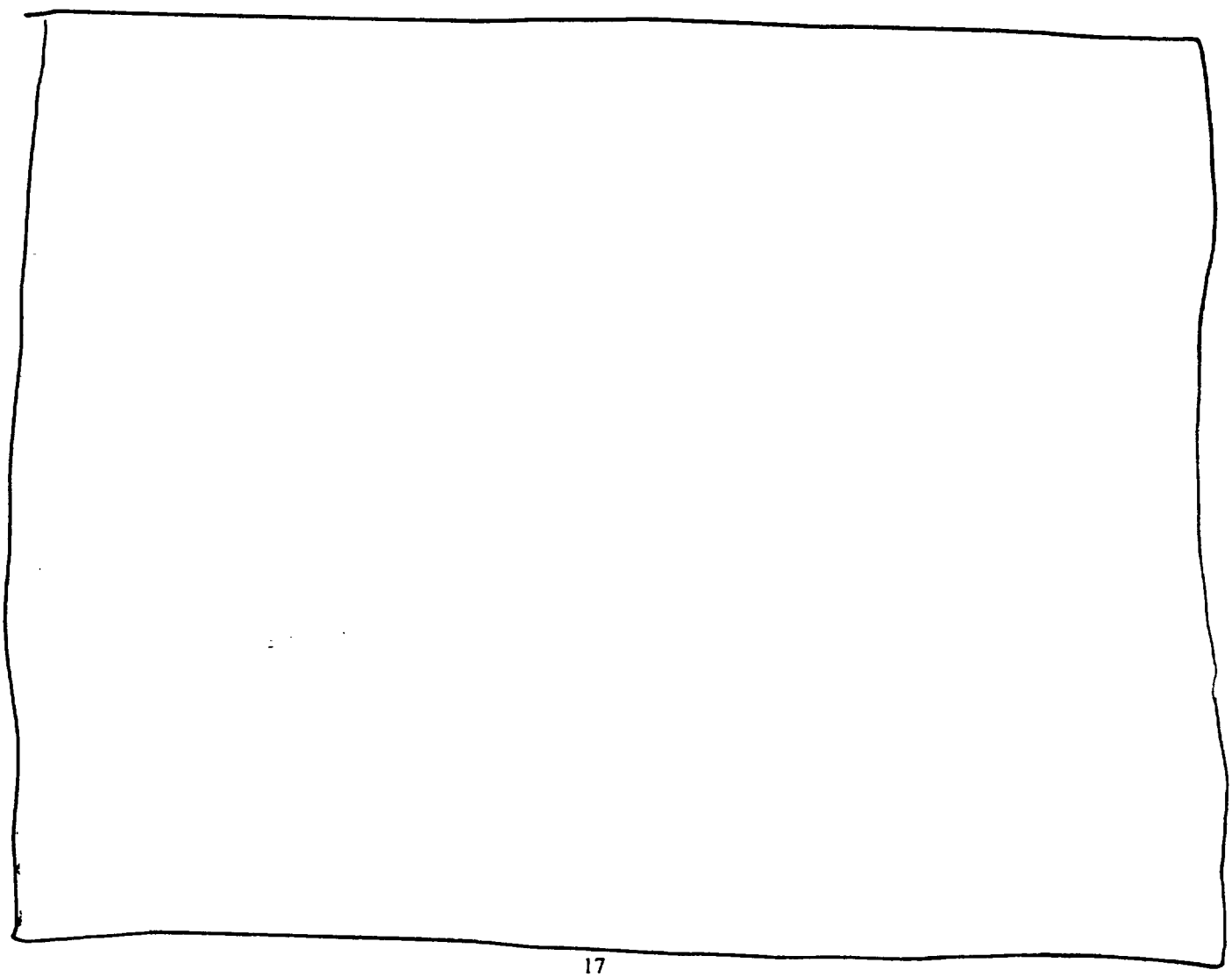
(1) **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (including methicillin-resistant strains), *Staphlococcus epidermidis* (including methicillin-resistant strains). *Streptococcus agalactiae*, and *Streptococcus pyogenes*, including cases associated with concurrent bacteremia with these microorganisms.

14 *pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.*

(90%) in the protocol. The reason for the difference is unexplained in this NDA. Bacteriological eradication rate in the clinically and bacteriologically evaluable population is 67.4% in the Synercid group and 54.7% in the Comparator group. The 95% confidence interval for the difference is (-8.4%, 33.8%). The bacteriological efficacy rates by pathogen in the Synercid group for the clinically and bacteriologically evaluable population at test of cure are 22/34 (64.7%) for *Staphylococcus aureus*, 2/3 (66.7%) for *Streptococcus agalactiae*, and 10/10 (100%) for *Streptococcus pyogenes*.

Safety

Drug related adverse events were twice as common in the Synercid group as in the Comparator group for non-venous adverse events and almost three times for venous adverse events. Study drug discontinuation due to adverse events also five folds more frequently in the Synercid group(24.2%) than in the Comparator group (5.0%). The majority ($\geq$ 80%) of adverse events were mild or moderate in intensity. However, more patients in the Synercid-treatment group reported moderate or severe events.



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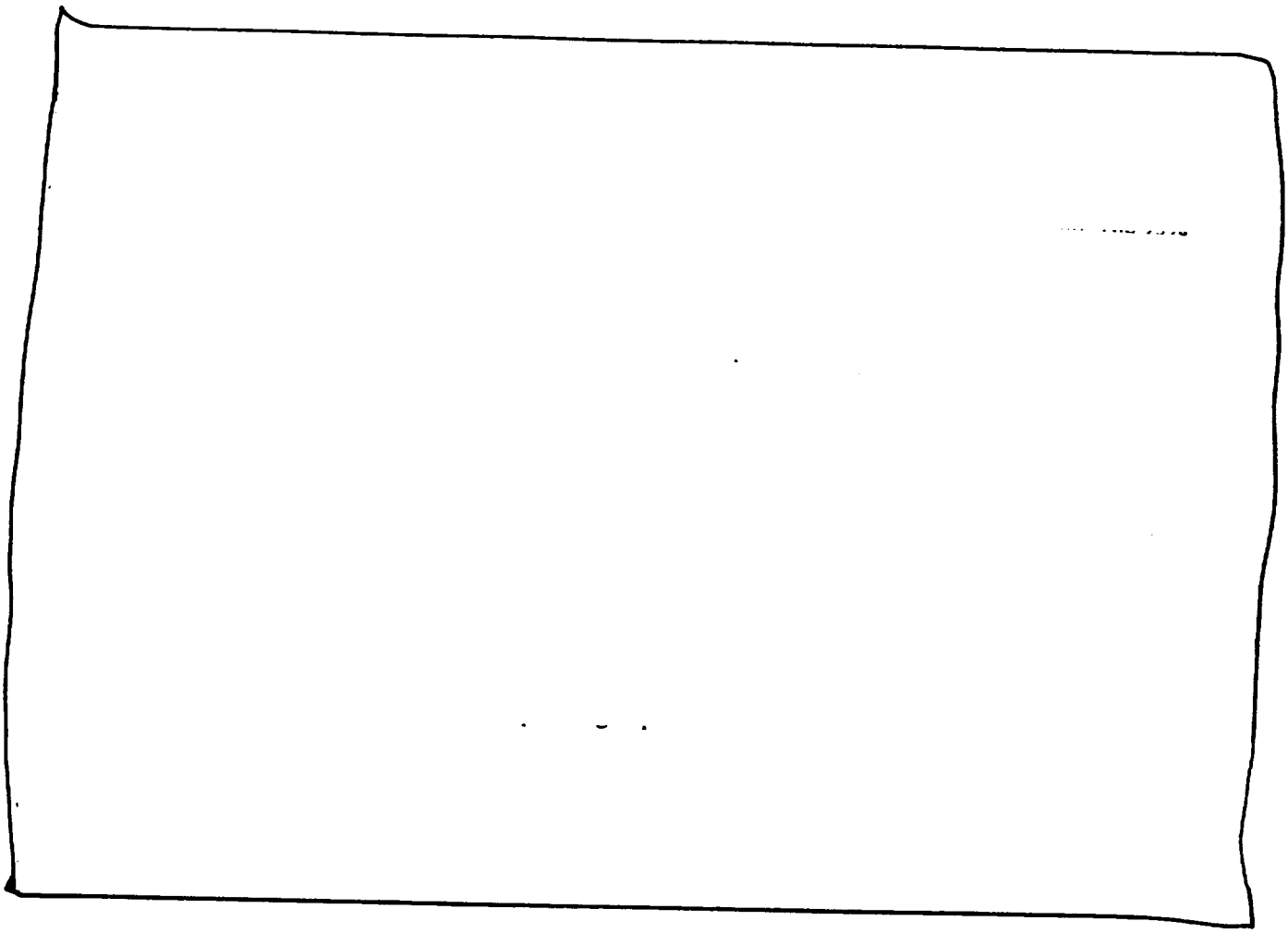


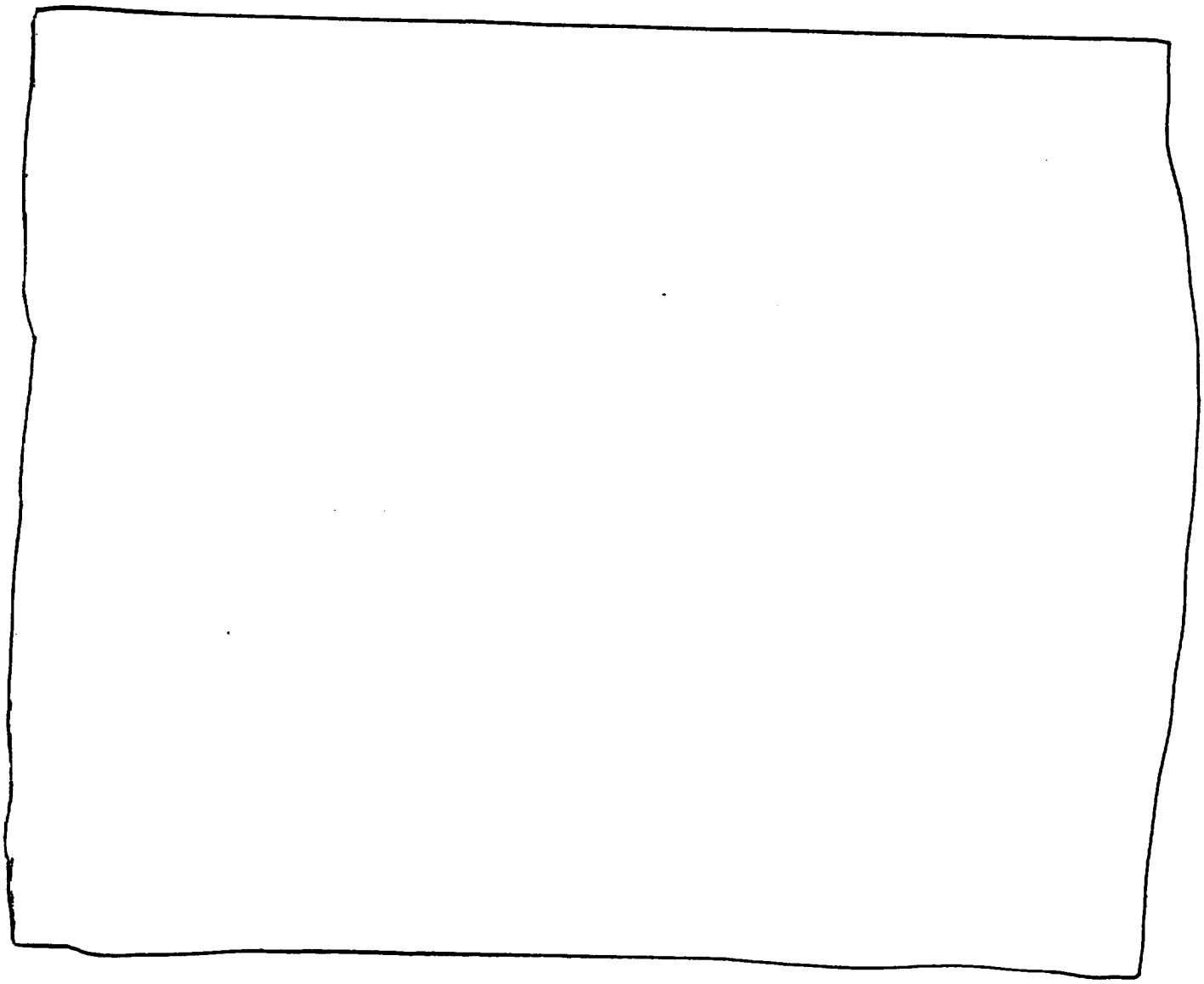
5. Statistical Reviewer's Overall Assessment

Complicated Skin and Skin Structure Infections (Studies 304 and 305)

The evaluability rates in both studies are relatively low. Many patients are non-evaluable because of violation of inclusion criteria or insufficient efficacy data. Demographic characteristics and risk factors between the evaluable population and non-evaluable population were compared and no statistically significant differences were noticed. Patients in the two treatment groups were also comparable.

Among the evaluable population, the clinical success rates of synercid and its comparator are lower than what was expected in the protocol. The reason is unknown. But, the 95% confidence intervals of the difference in Clinical Success Rates between the two treatment groups in the clinically evaluable population fall within the lower bound of -20% to establish the equivalence as specified in "Points to Consider" of DAIDP, FDA.

Drug related adverse events were much common in the Synercid group than in the Comparator group for both venous and non-venous adverse events. Study drug discontinuation due to adverse events was also much common in the Synercid group than in the Comparator group. The majority of adverse events were mild or moderate in intensity.



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